# DIABETES MELLITUS

*Principles and Treatment*

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## *Principles and Treatment*

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# Foreword

I appreciate the privilege of congratulating Dr Duncan on his growing attainments in clinical medicine and on the authorship of the present work The practical purpose of such a book is to teach the treatment of diabetes Though there are other good books on this subject, a new one is not superfluous but is a needed addition to the weight of authority against wrong doctrines The subject is controversial at a time when it should already have been clarified Mortality and disability remain high when they should be negligible Diabetes may be ranked as the worst treated of all diseases in relation to the knowledge and means available for its control Granting the part played by ignorance and carelessness of patients, there is need of more warning against the widespread fatal errors of physicians

The three main contributions of my early research can be claimed to have stood the test of time First, the reduction of total calories and body weight diametrically contradicted the previous universal high calorie high fat tradition which aimed at maintaining the highest possible weight The ideal of control was set up in cases previously classed as uncontrollable For the first time diabetes was linked with total metabolism, beyond the narrow glucose metabolism Second, the long familiar progressive loss of tolerance occurring in uncontrolled diabetes was elucidated by the experimental and clinical explanation of hydropic degeneration as a remarkable example of anatomic breakdown of an endocrine organ by functional over strain This degeneration and loss of beta cells was shown to be prevented by the same diet plan which controlled diabetic symptoms Immediately after the discovery of insulin, it was further shown that insulin administration cannot only prevent but also reverse this process so that the vacuolated cells regain granulation On this evidence was based the first affirmation that diabetes is not spontaneously or inevitably progressive Third, it was learned, first in dogs and then in young patients, that diabetes is still progressive when the blood sugar remains high, even without glycosuria The resulting first advocacy of normal glycemia as the standard of control has been repeated in many of my publications since that time This influence of hyperglycemia has lately been fully confirmed, particularly by Lukens production of hydropic degeneration and permanent diabetes in normal cats by continued large glucose injections The original postulate of connection between hyperglycemia and diabetic complications has theoretical and clinical support

Immediately after the introduction of insulin the theory was proposed that treatment might consist in giving enough insulin to metabolize the *requisite quantity of foodstuffs*, without regard to urine or blood tests The writers who have subsequently adopted and publicized this view are classifiable in three groups First, a small number use a few years of observation as basis for the claim that full and continuous health is provided by insulin dosage which maintains normal weight and absence of acidosis, with complete disregard of diet restrictions or laboratory tests A second group contradict the first group with long term observations showing that most or perhaps all patients thus treated ultimately fall victims of complications, but also that controlled diabetics have a similar statistical liability to the same complications, which therefore are regarded as inevitable and inherent in the disease rather than in the treatment A third group occupy a twilight zone, being satisfied with various degrees of control of sugar in urine and blood, often fearing hypoglycemia more than hyperglycemia and considering normal glycemia as risky or detrimental in some cases In actual practice, the result of prevalent teachings has been to include the majority of physicians in this country and throughout the world in this third group

My own attitude toward this literature may likewise be stated in three parts (a) While the appearance of gross complications may be deferred for twenty or more years, they ultimately occur in most and probably all uncontrolled diabetic cases Occasionally there is opportunity to see the onset of a complication after prolonged hyperglycemia with little or no [illegible] made normal Since

insulin daily, such a degree of prolonged deficiency of a vital hormone should not be expected to be harmless (b) I hazard the opinion that statistics proving similar incidence of complications in controlled and uncontrolled diabetes are nonexistent In other words, the cases listed as controlled by these writers have not been controlled in any proper sense of the word This criticism is *not mere hair splitting and does not refer* to brief or slight accidents of control The occurrence of a typical complication is *ipso facto* proof of lax treatment in the sense of gross and prolonged elevations or fluctuations of blood sugar, with the specific tissue malnutrition which they signify (c) This opinion is derived from thirty five years of clinical experience, which has comprised numerous complications occurring in *seemingly well nourished patients*, *without acidosis* and with excellent subjective feelings under various degrees of lax treatment, but not a single example in well controlled cases either with good nutrition under insulin or with severe undernutrition in the time before insulin It should furthermore be emphasized that, apart from a few exceptionally labile cases, properly managed control with insulin does not

burden patients with serious hardships or with the supposed danger of hypoglycemia

This statement applies not to the ordinary senile events occurring at natural ages, but to all typical diabetic complications, particularly the premature and excessive arteriosclerosis It comprises the uniform prevention of these lesions in early or youthful cases, the frequent but not invariable arrest of processes already active and the apparent halting of arteriosclerosis even in an advanced stage, so that no such case has gone on to gangrene and (barring one traumatic accident) no patient who had previously lost one leg has ever developed gangrene in the other Therefore for many years I have promised every cooperative patient a full lifetime of health, and I have had a standing challenge to family physicians and the various consultants who see these patients to report a single occurrence of any of the familiar complications, and nobody has yet shown an exception Such a sweeping claim was at first qualified by recognition of the frequency of peripheral vascular disease, sometimes entailing gangrene, among the nondiabetic population, and the consequent likelihood of this nonspecific process in occasional diabetics, so that the absence of any such examples to date has seemed noteworthy As mentioned, the guide in diabetes has been solely metabolic normality as judged by the most delicate known index, namely the blood sugar The guidance has disregarded incidental or secondary manifestations in the confidence, for example, that normal lipid metabolism is assured by control of the general disorder rather than by limitation of dietary cholesterol

Briefly, then the therapeutic principle in diabetes is the same as in any other disease The patient being abnormal, the physician's duty is to make him normal The means are available in diet and insulin It is tragic that the great discovery of insulin should have been used for carelessness instead of thoroughness of treatment Dr Duncan's book will place the issue on permanent record for future judgment of responsibility on one side for a mistaken dogma of preventability, or on the other side for literally millions of preventable tragedies of blindness other disabilities and premature deaths world wide throughout the past quarter century

Dr Duncan has distinguished several eras in diabetic treatment, but there should be the utmost awakening to the revolutionary epoch which lies ahead, in which the ideals will receive practical application so as to abolish all complications Perhaps the carefully ordered life of the diabetic may even set the example for longevity and freedom from arterial and organic degenerations beyond the present average among the general population

FREDERICK M ALLEN

# Preface

The objectives in preparing this volume have been twofold, first, to bring together and correlate up to date principles in the understanding of and in the treatment for diabetes mellitus and, second, to deal with this disease and its complications in such a manner that physicians and students may find herein a practicable and simplified outline of therapy

In fulfilling these objectives it has been necessary to cover quite a wide range, touching on nearly every specialty in Internal Medicine, as well as making excursions into the fields of Physiology, Physiological Chemistry, Pathology, Surgery, and Dietetics We have avoided as much as possible *controversial issues and multiplicity of theories and practices, by giving* most emphasis to known pathologic changes, to known phenomena influencing therapy and by outlining in considerable detail the practical measures, including the simplified Food Exchange System recently adopted by the American Diabetes Association, which have proved most useful in our experience

No apology is offered for frequent repetition of important concepts It is by this process that those physicians and students who do not see large numbers of diabetic patients will quickly grasp the relative importance of the facts presented

Illustrations have been used freely, especially in depicting the pathologic changes associated with diabetes Detailed considerations are given to the many facets of therapy and a considerable section of the book has been devoted to the complications—chronic and acute—of diabetes

All of the references needed to serve the practical purposes of our objectives are included This, of course, is by no means a complete bibliography of the subject

Reasonable calculations indicate that there are between one and one half and two million diabetic patients in this country Also, approximately 25 per cent of the total population have diabetic relatives These facts indicate the enormity of the overall problem presented by diabetes Our responsibilities embrace the early detection of the diabetes, adequate treatment a continuous educational program, the encouragement of research into the hidden mysteries of the disturbed physiology as encountered in diabetes and the prompt but wise clinical application of every advance achieved

I wish to express my sincere appreciation to my colleagues for their cooperation in this enterprise I am especially grateful to Dr A Reynolds

Crane, Pathologist to the Pennsylvania Hospital, for his constructive criticism and for several of the illustrations depicting pathologic changes characteristic of diabetes, to Dr John B Flick for his interest and efforts in behalf of our surgical patients, to Drs John B Alexander and Henry Russell for assistance in compiling data, and to Drs Frederick M Allen, Samuel Soskin and Joseph H Barach, Mr H H Marks and the U S Department of Public Health for permission to reproduce illustrations and other data from their publications

For painstaking and efficient secretarial service we are especially indebted to Miss Loretta M Stieber, and to Mrs Dorothea E Duncan for her very able assistance with the manuscript

To those who collaborated with me in the writing of this book I am especially indebted not only for this immediate enterprise but for the years of interest and work which they have devoted to making the lot for the diabetic patients a better one.

To the Dietary and Nursing Departments and to the many workers whose names do not appear but upon whose teachings and writings we have drawn in the fulfillment of our objectives, I am grateful

To Dr Frederick M Allen, with whom I spent two happy and profitable years, I owe much and I am especially grateful to him for his introduction to this volume

The cooperation and happy relations with the W B Saunders Company have lightened greatly the labor of preparing this work in its final form

GARFIELD G DUNCAN

*April, 1951*

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CHAPTER I

# Diabetes Mellitus

## 1 DEFINITION

Diabetes mellitus is a chronic disease manifested by multiple disturbances in the metabolic processes of the body. It is the result of a decrease in the production of endogenous insulin, or of other changes which increase, to a marked degree, the need for insulin. These features singly or in combination produce a relative or absolute *insufficiency of insulin* and account for the far reaching pathologic and clinical changes characteristic of this disease. Following promptly upon the development of hypoinsulism, disturbances in the metabolism of *carbohydrate* become apparent. The concentration of sugar in the blood increases above normal—*hyperglycemia*—and sugar appears in the urine—*glycosuria*. The frequent passing of large volumes of urine—*polyuria*—ensues. Dehydration, and the simultaneous loss of minerals, and loss of flesh follow in spite of excessive hunger—*polyphagia*—and thirst—*polydipsia*. As the loss of sugar increases *protein* is drawn upon in an attempt to replace sugar, to supply energy and, as a result, a negative nitrogen balance ensues, and wasting of muscle becomes prominent. Also the catabolism or breaking down of *fat* is speeded up in direct proportion to the reduction of carbohydrate utilization. As the metabolism of fat is accelerated a point is reached when the acetone bodies are produced in quantities beyond the capacity of the tissues to utilize them and the excretion of acetone in the urine follows.

Unless these processes are favorably influenced by treatment they tend to progress until the full capacity of the kidneys to excrete acetone bodies is reached. It is at this stage that the retention of acetone bodies in the blood becomes detectable in increasing amounts. Unchecked, these processes, with great latitude in the ranges of progressiveness, will lead to a fatal outcome.

Stetten[1] in investigating biologic processes by the isotope technic, has shown that under normal conditions a considerable portion of the body fat is broken down and resynthesized daily and that insulin is quantitatively more involved in the synthesis of fat from carbohydrate than it in the synthesis of glycogen. He found that about ten times as much goes into the formation of fat as into the formation of glycogen. In

*diabetic*, both of these processes—fat and glycogen production—are interfered with to a great degree and sugar, normally used in fat and glycogen production, is not utilized but accumulates in the blood and is excreted It is clear why the untreated diabetic patients lose weight so rapidly and why they gain so readily when insulin is supplied It is apparent that diabetes disturbs not only carbohydrate but protein, fat and total food and tissue metabolism as well—a fact that Allen has postulated for many years

*The disturbances in metabolism in diabetes* are remarkably accelerated and increased in degree by *acute infections* and *toxemias* It will be observed in the pages which follow that facilities now at hand have reduced almost to the disappearing point the risks which these complications formerly held Fifty years ago, Joslin[2] reports, 63 8 per cent of the patients died of diabetic coma, whereas now a death due to this complication is rare (1 9 per cent)

Formerly, attention was focused on the changes recorded above and *their immediate ramifications The picture has changed Diabetes, by lending* itself well to control with diet and insulin, has been subdued and life has been remarkably prolonged As the acute difficulties yielded to therapy and longevity was improved chronic changes became more and more evident *until now degenerative diseases have replaced acute complications as* the most common causes of death in the diabetic population We refer especially to premature arteriosclerosis and the hazards it presents Prominent among these is insufficiency of the coronary circulation Occlusive processes involving one of the coronary arteries have become the most common causes of death of adult diabetic patients Arterial sclerosis and retinal hemorrhages, intercapillary glomerulosclerosis and the diabetic neuropathies, also degenerative in nature, have assumed positions of increasing importance in the diabetic population Peripheral vascular disease continues to be a great hazard The great reduction of the mortality from diabetic gangrene does not mean that the underlying cause has been conquered Quite the contrary, peripheral vascular disease in diabetics is more prevalent than ever This is not surprising with the average age at death now being sixty four instead of forty four years (1898–1941) [2] Methods of treating the complications which immediately threaten life have improved to such a degree that a false sense of security is understandable, but nothing should detract attention from the underlying menace of arteriosclerosis and from attempts to solve the problems it poses

The understanding of *uncomplicated diabetes* and the individualized considerations necessary, the early recognition of and treatment for *acute complications*—ketosis, infections, thyrotoxicosis, etc —and the acceptance of the challenge which the *degenerative diseases* present *are essential if* maximum benefit is to accrue for these patients

*All are subject to undulations concomitant with complications, changes in endocrine and physical activities, as well as changes in diet*

## II PROGRESS IN THE UNDERSTANDING OF DIABETES

**The Pancreas and Diabetes.** *Participation of destructive processes* in the pancreas was observed in a diabetic patient by Cawley in 1788 but the appreciation of this association was not comprehended until in 1889 when Von Mering and Minkowski discovered that diabetes followed the experimental removal of the pancreas They established the doctrine of the internal secretion of the pancreas In 1901 Opie put forward the hypothesis that diabetes was associated with alterations in the islets of Langerhans of the pancreas Allen showed that changes in the islets in partially depancreatized dogs could be produced by alterations in diet, hydropic degeneration and loss of the functioning islet cells could be brought about by overfeeding but this process could be reversed by restricting the intake of carbohydrate and calories if the degenerative changes had not progressed to an extreme degree

*Then, in 1921,* Banting and his colleagues recovered insulin from the pancreas, and proved that with this agent successful control of the hyperglycemia and glycosuria of diabetes could be attained At last there was no controversy The pancreas and its internal secretion—insulin—are inextricably involved in diabetes Even when diabetes is produced experimentally it is the changes in the pancreas that cause permanent diabetes Alloxan which selectively destroys the insulin producing cells of the pancreas causes diabetes by doing so Also, tumors of the islets of Langerhans produce enormous amounts of insulin as do metastatic nodules of these growths Finally, removal of the entire pancreas in the human causes diabetes Diabetes produced in this manner is a much milder form of the disease than might be expected It is surprising that a depancreatized man needs only 20 to 50 units of insulin daily to maintain good control of the diabetes which results *Is this because an anti insulin mechanism or factor* is also removed with the insulin producing portion of the gland? There is some evidence that this is so[5] but attempts to isolate a hyperglycemic factor, so far, have been futile

*When the pancreas* is the only endocrine gland to be affected in causing diabetes, as is the case when a pancreatectomy is performed a mild diabetes results When, however, diabetes is precipitated by a primary excess

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[illegible] food intake and a reduction in [illegible]

diabetes that is readily controlled by a modest [illegible] reduced food intake and without treatment with insulin These patients become sensitive to insulin as their weight decreases but they lose this advantage if they permit obesity to recur

of anterior pituitary or adrenal hormone a more severe form of the disease develops and large amounts of insulin are usually needed to preserve good health. Also, the temporary diabetes resulting from injections of adreno-corticotropic hormone (ACTH) is relatively resistant to insulin.

Following removal of the pancreas from the dog the blood sugar rises above normal, the glycogen stores, particularly those in the liver, become depleted and sugar is lost in the urine in large amounts (Table 1). As the diabetes remains unchecked nitrogen excretion in the urine increases, indicating a sacrifice of protein in an attempt to meet the deficiencies incurred by the reduced metabolism of carbohydrate. The synthesis of fat is reduced drastically and the catabolism of fat is increased. The latter process becomes intensified and eventually to a degree when more acetone bodies are produced in the breakdown of fat than can be oxidized. As a result acetone appears in the urine and, barring relief from treatment, acetone bodies eventually accumulate in the blood, giving rise to ketosis

TABLE 1

Some Results Following Removal of Pancreas

| |
|---|
| Hyperglycemia |
| Glycosuria |
| Reduced glycogen—liver, muscle and skin |
| Reduction of Respiratory Quotient |
| Relative constancy between nitrogen and glucose excretion |
| Increased nitrogen excretion in the urine |
| Acetonuria |
| Dehydration |
| Demineralization |
| Ketosis |
| Death—usually within 4 to 14 days unless treated |

which, in the advanced stages, causes coma and death following a progression of the derangements mentioned above and the dehydration, hemoconcentration, loss of base, and peripheral vascular collapse which are associated with them in the final stages.

**Pituitary Gland and Diabetes.** The anterior pituitary gland is the major coordinator of the endocrine glands. As such, it has widespread influence on carbohydrate metabolism. One of the uncommon causes of diabetes is an hormonal imbalance associated with basophilic adenomas of the pituitary gland. Houssay[6] (1936) observed that the removal of the pancreas from an animal deprived of its pituitary gland caused a more attenuated diabetes than was the case when a normal dog was subjected to pancreatectomy. Evans and Houssay caused a transitory diabetes in dogs by injecting crude extracts of the anterior pituitary gland. Young,[7] by pyramiding the dosage of such extracts, produced, in adult dogs, a permanent diabetes. Destruction of the islets of Langerhans occurred as a res... of the administration of pituitary extracts. Haist[8] prevented the d...

of Addison's disease and diabetes The effects of increased adrenal cortical hormones are illustrated in cases of Cushing s disease

Experimental studies and the clinical evaluation of cases of disturbed adrenocorticotropic hormone have aided in the understanding of the part played by the adrenal cortex in diabetic and nondiabetic individuals The adrenal glands influence greatly the availability of glucose and its utilization in the tissues Both of these features are of importance in clinical diabetes

**The Thyroid Gland and Diabetes** Clinically, the thyroid gland affects carbohydrate metabolism *in direct proportion to the metabolic rate* over which it maintains a most important control In thyrotoxicosis carbohydrate is absorbed more rapidly than normal—a feature which may lead to faulty interpretation of glucose tolerance curves (see p 79) Diabetes tends to be intensified by excessive thyroid therapy or thyrotoxicosis

TABLE 3

*Alterations in Function of the Thyroid Gland and Diabetes*

| | THYROTOXICOSIS | CONTROL OF THYROTOXICOSIS |
|---|---|---|
| Diabetes | *Aggravated* | *Ameliorated* |
| Blood sugar | Readily elevated | More stable |
| Glycosuria | Aggravated | Tends to be corrected |
| [illegible] | [illegible] | Depressed |
| [illegible] | [illegible] | Normal or slightly decreased |
| [illegible] | [illegible] | Normal or slightly decreased |
| [illegible] | [illegible] | Normal |
| [illegible] | [illegible] | Normal |
| [illegible] | [illegible] | Reduced |
| [illegible] | [illegible] | Prolonged |

and the opposite is the case with the development of hypothyroidism (Table 3) However, the thyroid hormone is not a diabetogenic hormone in the same sense as are the pituitary gland and the adreno cortico steroids It affects carbohydrate metabolism and hence diabetes through its influence on the rate of tissue metabolism Thyroidectomy does not alleviate a total diabetes (Lukens and Dohan[12])

**Evolution in Therapy for Diabetes** The construction of the bases upon which the present therapy for diabetes rests has entailed much research which has been rewarded at times with sudden great advances with interim periods during which a slower but never completely static evolutionary change took place

Dr Elliott P Joslin has emphasized these different phases of progress by naming the respective eras or epochs after the physicians responsible for the new developments in the understanding of and therapy for diabetes The eras so depicted are as follows

| | |
|---|---|
| Naunyn era | 1898 to 1914 |
| Allen era | 1914 to 1922 |
| Banting era | 1922 to 1936 |
| Hagedorn era | 1937 to 1943 |
| Best era | 1944 to date |

### *The Naunyn Era (1898–1914)*

Naunyn was the foremost authority on diabetes of his time He influenced greatly the advancement of clinical and experimental knowledge of this disease He was well aware of the hereditary basis of diabetes and was, until 1886, the champion of a strict carbohydrate free diet Later, he supported a more rational treatment reckoning the diet on the tolerance for carbohydrate and caloric requirements of each patient To Naunyn's pupils we owe much of the early understanding of clinical acidosis Naunyn introduced the term "acidosis"

Naunyn s plan of treatment for diabetes was that of a gradual withdrawal of the carbohydrate, the increase of the diet after glycosuria had subsided to 35 to 40 calories per kilogram of body weight and about 125 gm of protein with the carbohydrate allowance being established below the amount which would cause glycosuria, occasional fast days were employed when glycosuria was persistent However, prolonged undernutrition or the loss of more than 2 kilograms of weight was avoided Diets high in protein and fat content were the rule The administration of large doses of sodium bicarbonate in cases of acidosis, brisk exercise for the patient having mild diabetes and much less physical activity when the disorder was of a severe degree were advocated

Naunyn had a strong conviction that diabetes should be energetically treated as soon as the diagnosis was made With this concept present day authorities on the subject are agreed

### *The Allen Era (1914–1922)*

Allen contributed greatly to the knowledge of the pathology of diabetes His proofs of the effects of changes in total metabolism on diabetes are of outstanding clinical importance The principles of undernutrition as a therapeutic measure in the treatment for diabetes are just as true today as when they were introduced in 1914 Fortunately they need not be as rigorously employed as it was necessary to do in the pre insulin days, Allen emphasized the value of a reduction in the total caloric intake and employed this measure to such a degree that one or two fast days were included per week with submaintenance diets on the remaining days when the diabetes could not be controlled by less strict means In this manner many patients were kept alive who would otherwise have been lost before insulin became available Allen showed that loss of weight from uncon

CHAPTER II

# History of Diabetes

*Diabetes mellitus has presented clinician and investigator* with the problems of aberrations of metabolism, the wrestling with which has increased understanding of metabolism in general and to a degree much more advanced than would have been so if the demand for solution had not been ever present in the form of serious clinical complications The history of *diabetes as presented by Allen*[1] *relates that in the Ancient Period* "the passing of frequent and large quantities of urine" was recorded in the papyrus Ebers, an Egyptian medical journal already old in the time of Moses (Saundby) 'Polyuria without pain but with emaciation and danger" was recorded in reference to diabetes by Celsus (30 B C–50 A D) *The Ionic Greek name diabetes, meaning "to run through a siphon,"* was given by Aretaeus (30–90 A D), who also wrote of the "progressiveness of diabetes" and of the 'fatal prognosis" associated with this disease Diabetes was described as a "disease of thirst" by Tchang Tchangking (200 A D) who observed a patient, suffering from this disease, drink ten *quarts of water per day with a relative degree of polyuria* "Excessive appetite" was recorded as a symptom of diabetes by Chinese writers about 600 A D The "sweetness of the urine" of diabetic patients was first mentioned by Ayur Veda Susruta (Chunder Rose) Ants were observed to flock around the patients' urine and "weakness, emaciation, polyuria and *carbuncles" were associated with diabetes.*

*Diabetic gangrene* was described as such by Avicenna (980–1037 A D) *Furunculosis* and *tuberculosis* were recognized as characteristic complications of diabetes in the fifteenth century Crystals were formed on the evaporation of the urine of a diabetic patient by Paracelsus (1493–1541), who mistook them for "salt," and *lipemia* was first associated with diabetes by Helmont (1578–1644).

In the *Second* or *Diagnostic Period* Willis (died 1675) observed the urine of the diabetic patient to be "wonderfully sweet as if imbued with honey or sugar" Willis was the first to advocate a carbohydrate or un*dernutrition* "cure" The hereditary nature of diabetes was made clear by Morton (died 1698), and Dobson in 1775 grasped the fact for the first time that the sweetness of the urine was due to sugar Disease of the pan

creas was first described as occurring in a patient dying of diabetes by Cawley (1788). There were multiple pancreatic calculi and much destruction of pancreatic tissue. The adjective *mellitus* was added to diabetes by Cullen (1709–1790) to distinguish the disorder from diabetes insipidus. Francis Home, on adding yeast to urine of the diabetic patient, learned that the sweetness disappeared and at the same time established the fermentability of the sugar.

In the *Third Period* or *Period of Empiric Treatment*, Rollo (1796) restricted the diet to animal food and a few green vegetables and he was the first to note and record the significance of *diabetic cataracts*. The "odor of decaying apples" was noted on the breath of a young diabetic patient by Marshal (1799). The sugar in the urine was identified as *glucose* by Chevreul (1815) and Gregory (1825) described the differences between diabetes mellitus and diabetes insipidus. Prout advocated "restriction of protein" in the treatment for diabetes. He introduced washed bran as an adjunct in diet therapy and he described *coma* as a typical and end result of diabetes.

In the *Modern* or *Experimental Period* Gregory demonstrated a fermentable sugar in the blood of diabetic patients, Trommer in 1841 and Fehling in 1850 introduced qualitative tests for sugar in the urine, Claude Bernard (1855) founded the theory of sugar formation from glycogen and postulated that increased blood sugar levels were due to overproduction of sugar by the liver, Mialhe (1845) recommended the use of alkali in the treatment for diabetes. Bouchardat (1806–1886) substituted alcohol and fat for carbohydrate, he individualized his patients' needs, advocated small diets with an occasional day of fasting and introduced thrice cooked vegetables and gluten bread. He observed advantages of physical exercise and advocated the daily testing of the urine for sugar. *Acetone* was recovered from the urine of a patient in diabetic coma by Petters in 1857 and Kussmaul in 1874 described the type of breathing, which still bears his name, observed in patients in diabetic coma. Severely restricted diets, 'fast days,' physical exercise and insistence of complete freedom from glycosuria were standards used by Cantani (1837–1893). That all diabetes was pancreatic in origin was hypothecated by Baumel. Ehrlich noted glycogenic degeneration of renal tubules in diabetes and Kutz (1845–1893) identified oxybutric acid in the urine of diabetic patients. He also observed that exercise helped patients having mild diabetes but that the opposite was true if the diabetes were severe.

*Islet cell formations* in the pancreas were discovered by Langerhans in 1869. Diabetes following pancreatectomy in a dog was observed by von Mering and Minkowski (1889) who established the doctrine of the internal secretion of the pancreas and it was Minkowski who discovered the low $CO_2$ combining power of the blood in diabetic coma. Naunyn introduced the term *acidosis*; he recognized clinical *renal glycosuria* and he employed

diets with low carbohydrate, low protein and high fat contents in the management of diabetes *Hydropic degeneration of the islets of Langerhans* in diabetics was reported by Weichselbaum and Stangle but it was *Opie, in 1901,* and Ssobolew who proposed the theory that diabetes was "due to alterations in these islets" Roulston and Woodyatt, Newburgh and Marsh Petren, Wilder and Shaffer, employed diets with high fat content but it was with Allen's introduction of *undernutrition* as a *therapeutic measure in treating diabetics* that the first really great advance in therapy was made.

Important advances including and subsequent to the introduction of Allen's undernutrition regimen will be dealt with in considerable detail throughout this book but for the sake of completeness the more important advances in the understanding of and treatment for diabetes are listed here

Joslin and others confirmed the benefits of Allen's undernutrition therapy which rapidly became the treatment of choice Allen presented the hypothesis that diabetes was 'a disorder of total metabolism and not of carbohydrate metabolism alone"

Then *insulin* was discovered in 1921 by Banting and Best This discovery dwarfed in importance all others, especially as they dealt with severe and complicated diabetes A trend to more liberal calories and carbohydrate promptly ensued and gradually as the effects of insulin and other modifications of therapy which insulin permitted, the entire outlook for the diabetic patient became so altered that it is difficult in 1951 to envision that only a few years ago semi starvation was the price patients with severe diabetes had to pay to remain alive Even this price was of no avail in cases of children and many of the emaciated adult diabetic patients

*Removal of the pituitary gland from a dog increased the animal's sensitivity* to insulin (Houssay and Magenta 1924) but this hypersensitivity was diminished by treatment with pituitary preparations (Houssay and Potick, 1929) The severity of diabetes was decreased by hypophysectomy (Houssay and Biasotti 1930) and a transitory diabetes was provoked by injecting a normal dog with anterior pituitary extract (Houssay, Biasotti, and Rieti, Evans, Bauman and Marini, 1932) and diabetes was made more severe by injecting anterior pituitary gland extracts (Houssay and *Biasotti, Houssay,* 1936) Diabetes was attenuated by the removal of the adrenal cortex of depancreatized cats (Long and Lukens, 1936) Then, in 1937, Young experimentally produced permanent diabetes by injecting intraperitoneally increasing amounts of *crude extract of the* anterior pituitary gland Experimental diabetes was made more severe by giving large doses of cortin in depancreatized adrenalectomized dogs (Lukens and Dohan 1938)

*Protamine insulin* was discovered by Hagedorn (1936) and the improved *combination protamine zinc insulin* was made available as a result

*of the investigations of Scott and Fisher (1936).* The latter provided a stable product of slow and prolonged action

Restoration of hydropically degenerated pancreatic islets by adequate insulin therapy (Copp and Barclay, 1923, Lukens and Dohan, 1940) and the protection from the diabetogenic effect of injections of pituitary extract by administering large doses of insulin, by a starvation regimen or by a high fat diet (Haist, Campbell and Best, 1940), added to our knowledge of this complex subject

The selective destruction of the beta or insulin producing cells of the islets of Langerhans by the intravenous injection of alloxan (Jacobs, 1937, Dunn and McLetchie, 1943, Bailey and Bailey, 1943, Goldner and Gomori, 1943) presented a new approach to the study of diabetes and possibly to its etiology Also, the administration of glutathione, a normal component of the body, protects against the diabetogenic effects of alloxan Alloxan can be derived from uric acid The development of hyperglycemia and glycosuria following injections of ACTH is reversed by administering glutathione (Conn, 1949).

Hyperglycemia, in cats, maintained by intraperitoneal injections of glucose, has been shown to produce diabetes and it has been demonstrated that control of the diabetes in the early stages reverses the pathologic processes and produces a cure (Dohan and Lukens, 1947)

*Tagging nutritional components of a diet with radioactive labels* and observing their behavior and fate is affording a means of making an infinitely more profound chemical analysis of disturbed values in diabetics than has been possible heretofore (Stetten, 1948) Hyperglycemia and glycosuria have been produced in rabbits by intraperitoneal injections of uric acid after reducing blood glutathione concentrations to a low level by means of a diet deficient in cystine and methionine (Lazarow, 1946, and Griffiths, 1948) The two principles of this process—glutathione and uric acid— are normal constituents of the human body One is tempted to speculate!

Hormonal imbalance and its management in pregnant diabetic patients (Smith, Smith, and Hurwitz 1944, White, 1948) and the importance of hypopotassemia immediately following therapy for diabetic coma (Guest, 1942, Holler 1946, Nadler *et al*, 1948) are among the significant advances in reducing the mortality rate from these complications The elaboration of the value of electrocardiography in detecting hypopotassemia during therapy for diabetic coma by Bellet *et al* (1950) also is of great clinical significance The far reaching benefits derived from sulfonamide and antibiotic therapies should be included in a listing of historical landmarks dealing with progress for the diabetic patient

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1940, and that an increase of 18 per cent could be expected by 1950, during which time the expected increase in the total population would be only 9 per cent It has been estimated that more than 4,350,000 of the present population of the United States would eventually become diabetic It is highly probable that the total number of diabetics has been underestimated The high incidence of diabetes found in the course of Selective Service examinations indicates a higher frequency of this disease among the younger age group than was formerly considered [3]

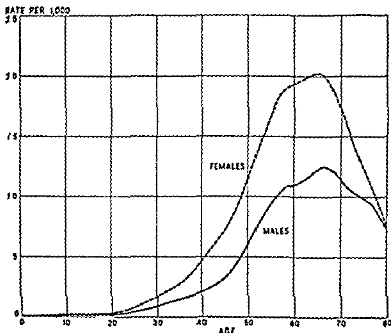



Fig 1 Diabetes onset rates per 1000 (Chances of becoming diabetic within the year of age) United States, 1935 1936 [4]

**Age and Sex.** The National Health Survey (1935–36) revealed that the incidence of diabetes increased steadily until the seventh decade of life in both sexes There has been no significant change so far in the twentieth century in the age at onset of the diabetes in any of the decades of life (Table 3) The peak incidence for the onset of diabetes for both sexes occurs between fifty and seventy years of life, as indicated in Figure 1

The constantly increasing life expectancy of diabetic patients on the one hand with no significant change on the other hand, in the age at onset of the diabetes, is a prominent factor in the increasing incidence of diabetes in the older age groups

Diabetes occurs more frequently in the female than in the male Marked

CHAPTER III

# Incidence of Diabetes

**Total Number of Cases.** Diabetes is more prevalent than ever before and the incidence of the disease, though not accurately known, is steadily increasing There are more than one million known diabetics in the United States in 1951, and newly identified cases are currently amounting to 55,000 annually [1] The *increasing incidence of recognized cases is due, in* part, to a newly awakened public interest and action arising from the educational activities of the American Diabetes Association and its subsidiary branches, and partly to the broadening scope of regular check up and insurance examinations Absolute increases in the incidence of diabetes are attributable to the greater numbers of our population in the older

TABLE 4

AGE AT ONSET OF DIABETES (JOSLIN)

| DECADES | PER CENT APPEARING IN EACH DECADE 1936–1938 | |
|---|---|---|
| | *Males* (1265 patients) | *Females* (1622 patients) |
| 1 | 6 7 | 4 6 |
| 2 | 9 0 | 6 2 |
| 3 | 8 6 | 6 2 |
| 4 | 13 1 | 11 0 |
| 5 | 19 8 | 21 0 |
| 6 | 22 1 | 28 1 |
| 7 | 16 2 | 18 1 |
| 8 | 4 3 | 4 1 |
| 9 | 0 2 | 0 1 |
| | 100 | 100 |

age groups, *to the improvement in treatment* which permits diabetics a span of life closely approaching that of the normal, and to the increasing number of young diabetics who marry and have children *who are more* likely to develop diabetes than are children of normal parents

Spiegelman and Marks[2] *estimated, on the* basis of a National Health Survey in a house to house canvas involving 800,000 families and 2,600,000 persons, that there were 500,000 diabetics in the United States in

1910, and that an increase of 18 per cent could be expected by 1957, during which time the expected increase in the total population would be only 9 per cent. It has been estimated that more than 4,350,000 of the present population of the United States would eventually become diabetic. It is highly probable that the total number of diabetics has been underestimated. The high incidence of diabetes found in the course of Selective Service examinations indicates a higher frequency of the disease among the younger age group than was formerly considered.[3]

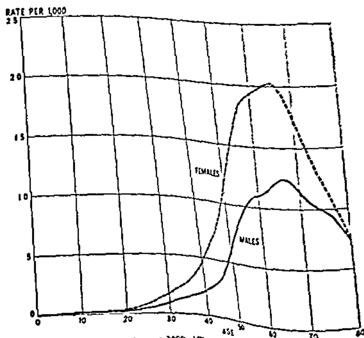



Fig 1 Diabetes onset rates per 1000 (Chances of becoming diabetic within the year of age) United States, 1935-1936

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Diabetes occurs more frequently in the female than in the

estimates that 2.1 per cent of the male population of 1946 will become diabetic and that 3.8 per cent, or nearly twice as many, of the female population will develop this disease. In the National Health Survey,[4] 9182 diabetics were encountered and 64.2 per cent of these were female. Women live longer and are less active physically than men and are more prone to become obese between forty and seventy years of age than are the men.

The chances of eventually becoming diabetic, by age and sex, are presented in Table 5.

The incidence of diabetes is higher in married than in single women[5] over forty five years of age and especially higher in women who have borne children. Married women who have had children weigh more than single women. This increased body weight undoubtedly influences the incidence of diabetes unfavorably. The security enjoyed by the average married woman over forty five years of age influences the likelihood of gaining in body weight and hence a greater likelihood of developing diabetes. There is an increasing incidence of diabetes in women over forty five years of age out of all proportion to that observed in the male population. The seriousness of the diabetic problem in women over forty five years of age is depicted in Figure 1. The increase in the mortality rate of this group over male diabetics of the same age is striking (Fig. 2).

TABLE 5

CHANCES PER 1000 OF EVENTUALLY BECOMING DIABETIC BY SEX AND AGE
UNITED STATES 1935 1936 (MARKS)[1]

| AGE | MALES | FEMALES |
|---|---|---|
| Under 15 | 22.1 | 41.5 |
| 15–19 | 22.4 | 42.0 |
| 20–24 | 22.6 | 42.3 |
| 25–29 | 22.8 | 42.6 |
| 30–34 | 22.8 | 42.6 |
| 35–39 | 22.7 | 42.2 |
| 40–44 | 22.4 | 41.3 |
| 45–49 | 21.9 | 39.4 |
| 50–54 | 20.7 | 36.2 |
| 55–59 | 18.1 | 30.7 |
| 60–64 | 14.8 | 23.8 |
| 65 69 | 11.3 | 16.6 |
| 70 74 | 7.7 | 10.0 |
| 75–79 | 4.6 | 5.2 |
| 80–84 | 2.0 | 2.0 |
| 85 89 | 0.4 | 0.4 |

**Occupation.** Diabetes is more prevalent in urban than in rural communities. This is true also of the mortality from diabetes, which is between 60 and 70 per cent higher in the former area. The disease occurs more frequently among the employing and professional groups and among those engaged in selling and serving food and drink.[6]

The mortality rates as applied to the various occupations illustrate well the beneficial effects of occupations calling for ample physical activity and at the same time highlight the hazards of ownership and other occupations in which there is relatively little need for much physical activity Hired help on farms do more physical work than the farm owner and are less likely to develop diabetes than their employers Mechanization of labor will tend to increase rather than decrease the incidence of this disease and the complications which arise as a result of it

**Race.** Members of the Jewish race, particularly women, and especially those over forty years of age, are more prone to develop diabetes than the population as a whole Jews comprise approximately 3 5 per cent of the population of the United States and yet among 5000 new diabetic patients Joslin found 810 or 16 2 per cent to be Jews It is conservatively estimated that diabetes is one and one-half times as common among the older Jews as it is in the average population This applies in all countries although probably is most clearly shown in Greater New York (Jewish Commercial Survey, 1931)

This racial predisposition has been attributed to persecution which prevented Jews from owning or tilling land, forcing them into more sedentary occupations Probably the most important cause is the in breeding of this race, with occupation and obesity as precipitating rather than essential causes The effects of occupation, prosperity and well being in predisposing to diabetes are exemplified in the higher incidence of diabetes in the Irish in the United States than occurs in the same race living in Ireland Diabetes is common among the Teutonic races and uncommon among the Slavs and Latins The Negro race was formerly, and erroneously, believed to be relatively free from diabetes With the improvement of social standing and prosperity with larger numbers of Negroes doing less physical work, obesity and diabetes have increased with greater frequency in the colored than in the white race Approximately 35 per cent of the patients attending the Out Patient Diabetic Clinic at the Pennsylvania Hospital are of the Negro race

Diabetes is relatively infrequent among the Chinese and Japanese and severe forms of the disease are unusual in these races

Estimates have been made that there were 300 000 diabetics in Germany in 1938, 150,000 to 200 000 in the United Kingdom in 1939

Diabetes rates at best are inaccurate In some countries the incidence is calculated most reliably by using the mortality rates The lack of uniformity in recording the causes (actual and contributory) of death makes most figures speculative

**Mortality.** Lack of uniformity in reporting causes of death detracts from the value of these vital statistics Often, the diabetes has not been recorded on the death certificate if the patient also had cancer This is but an illustration of how the record of the death of a diabetic may fail to

reach statistics dealing with diabetes Approximately two thirds only of the death certificates of diabetics contain a record of the diabetes Hence the recorded deaths of 3559 diabetic patients in Pennsylvania in 1948 may be one third lower than the actual experience The new death certificate form[6] should aid in correcting statistics dealing with diabetic patients in the future

The death rates from diabetes are higher in the United States than in any other country The census reveals that 36 311 persons died from diabetes in 1943 34,948 in 1944 35,160 in 1945, 34 731 in 1946, and 37,515 in 1947 These figures represent 27 1, 26 4, 26 6, 24 8 and 26 2 per 100, 000, respectively

TABLE 6

DEATH RATES FOR THE TEN LEADING CAUSES UNITED STATES 1945–47*

(Exclusive of stillbirths and of deaths among armed forces overseas Rates per 100 000 estimated mid year population excluding armed forces overseas)

| CAUSE OF DEATH | 1947 | 1946 | 1945 |
|---|---|---|---|
| ALL CAUSES | 1 007 8 | 997 6 | 1 061 8 |
| Diseases of the heart | 321 2 | 306 8 | 321 4 |
| Cancer and other malignant tumors | 132 4 | 130 1 | 134 4 |
| Intracranial lesions of vascular origin | 91 4 | 89 8 | 97 8 |
| Nephritis | 56 0 | 58 4 | 66 7 |
| | 46 6 | 46 2 | 51 4 |
| | 43 1 | 44 5 | 51 8 |
| | 33 5 | 36 4 | 40 1 |
| | 28 6 | 28 5 | 23 9 |
| | 26 2 | 24 8 | 26 6 |
| | 22 8 | 23 9 | 24 3 |

* After Vital Statistics—Special Reports National Summaries 31 (No 3) 22 (May 9) 1949

Diabetes ranks ninth in the list of major causes of death, 1945–1947 (Table 6), in contrast to twenty seventh place in 1900 It caused in 1943, three times as many deaths as tuberculosis in white women over forty five years of age[6] With improved therapy for tuberculosis and pneumonia, diabetes is certain shortly, to be the seventh major cause of death in all age groups and in both sexes

Provisional data indicate an increase in the death rate of 6 per cent for the country as a whole for 1949 over that of 1948[7]

The mortality rate of diabetes increases steadily until the eighth decade of life The older age groups have absorbed the increased mortality rates from diabetes This naturally follows the reduced rates in diabetics under fifty years of age, the aging of the population—diabetic and general—and the more frequent diagnosis of diabetes in elderly individuals The average age at death of diabetic policy holders of the Metropolitan Life Insurance Company had increased from 51 5 years in 1911 to 61 5 years in 1945

Sex exerts influences in the mortality rates as well as the incidence of diabetes. Over thirty four years of age the death rate in females exceeds *increasingly that of males as shown in Figure 2, until in the later decades* it is nearly twice that recorded for the males. This is, in more or less degree, the experience in other countries as well as in the United States and Canada.

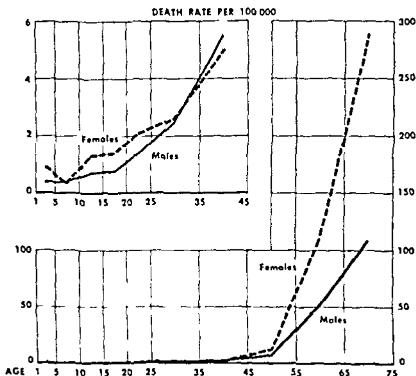



Fig. 2. Diabetes Death Rates by Sex and Age Among White Persons, Metropolitan Life Insurance Company Industrial Department, 1946 1948 indicate (1) a low rate in childhood and young adult life (2) a rapid acceleration of the death rate after forty five years of age in both sexes and (3) the increasing excess of rates for females over that of the males after forty five years of age, reaching nearly $2\frac{1}{2}$ times that for males between the ages of sixty five and seventy four.

(After Spiegelman, M., and Marks, H. H. Am. J. Pub. Health, 36 26, 1946.)

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| *Cancer and other malignant tumors* | *132 4* | *130 1* | *131 4* |
| Intracranial lesions of vascular origin | 91 4 | 89 8 | 97 8 |
| Nephritis | 56 0 | 58 4 | 66 7 |
| Accidents (excluding motor vehicle accidents) | 46 6 | 46 2 | 51 4 |
| Pneumonia (all forms) and influenza | 43 1 | 44 5 | 51 8 |
| Tuberculosis (all forms) | 33 5 | 36 4 | 40 1 |
| Premature birth | 28 6 | 28 5 | 23 9 |
| Diabetes mellitus | 26 2 | 24 8 | 26 6 |
| Motor vehicle accidents | 22 8 | 23 9 | 21 3 |

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DEATH RATE PER 100 000

Fig 2 Diabetes Death Rates by Sex and Age Among White Persons, Metropolitan Life Insurance Company, Industrial Department, *1916–1918*, indicate (*1*) a low rate in childhood and young adult life, (2) a rapid acceleration of the death rate after forty five years of age in both sexes and (3) the increasing excess of rates for females over that of the males after forty five years of age, reaching nearly 2½ times that for males between the ages of sixty five and seventy four

(After Spiegelman M., and Marks H H Am J Pub Health **36**:26, 1946)

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CHAPTER IV

# Etiology of Diabetes

## INTRODUCTION

The exact cause of clinical diabetes appearing spontaneously is unknown The circumstances which surround the incidence of this disease in certain groups, e g, diabetic families," obese persons, and the methods of producing diabetes experimentally, incriminate *heredity, obesity, damage to or loss of the insulin producing beta cells of the islets of Langerhans, hormonal imbalances* and other features inadequately explained Notable among the last mentioned are the extreme degrees of insulin resistance

Whatever factor or factors culminate in clinical diabetes, it is generally agreed that this disorder represents a disproportion between insulin need and insulin production and that this does not necessarily mean an insulin production below normal It is known that the demand for insulin often exceeds the amount necessary to control adequately the diabetes which results from a total pancreatectomy The totally depancreatized adult human develops a daily insulin requirement between 30 and 50 units[1] This is in contrast to the large number of diabetic patients needing more *than 50 units daily and especially those highly resistant to insulin who* may require several hundreds of units, or more, daily In alluding to the low insulin need of the depancreatized man we are aware that the number of such cases is exceedingly small, that the duration of life in the depan *creatized state* is *relatively* short, and that the nutritional status and the total metabolism are likely to be grossly disturbed Pancreatectomy seriously disturbs nutrition by reducing the absorption of fat and protein and this is doubtless a big factor In addition there is evidence that the removal of the pancreas with its alpha cells removes the source of a hyperglycemic factor Hence, if this is true, it explains why the totally depancreatized human needs less insulin than a diabetic who retains the potential possibility of producing an anti insulin factor

## PREDISPOSING FACTORS

**Heredity.** The predisposition to diabetes by heredity is established Superimposed upon an inherited inadequacy may be other precipitating or deciding factors notably obesity and much less frequently, endocrine dis

turbances Over 50 per cent of diabetic children have a family history of diabetes White and Pincus[*] to whom we owe the clear cut understanding of the hereditary basis of diabetes present as evidence of this conclusion (1) the almost simultaneous development of diabetes in identical twins, (2) the higher incidence of the disease among blood relatives of diabetics, and (3) the behavior of the incidence of diabetes in accordance with Mendelian patterns The Mendelian pattern depicts diabetes as carrying recessive characteristics *It is predictable that, (1) if both parents have diabetes all of their immediate offspring will have diabetes if they live long enough, (2) if only one parent has diabetes and the other parent is nondiabetic but has a diabetic father or mother, the chances are even that the nondiabetic parent is a carrier* A diabetic child of such a union would establish the nondiabetic parent as a carrier and that other children of this union stand a 50 per cent chance of developing diabetes The chances of the children of this union developing diabetes are less than 50 per cent if the nondiabetic parent who may or may not be a carrier, has a diabetic brother or sister If the nondiabetic parent has a distant relative with diabetes it is unlikely, but possible that the children will develop diabetes (3) if neither parent has diabetes but each had a parent who had diabetes the chances are 1 in 4 for the development of diabetes in their children, if a child of carrier parents develops diabetes the chances are 1 in 4 that the brothers and sisters will develop diabetes also, if a diabetic or diabetic carrier marries a nondiabetic from a nondiabetic family none of the immediate offspring will develop diabetes The breeding out of diabetes falls within the realm of possibility To achieve this a consistent union of descendants of diabetic patients with those of nondiabetic families for several generations would be essential

Granted an hereditary basis for diabetes exists, the onset of the disease is modified by body weight age endocrine disturbances, occupation, infections and, possibly, by race

**Obesity** It is known as a result of Allen's observations, which have been amply confirmed, that diabetes is ameliorated when the body weight is reduced by decreasing the caloric intake Also, the need for insulin increases remarkably with increasing body weight The *obese diabetic is relatively resistant to insulin* Nevertheless the obese diabetics, excepting those who have become obese by virtue of insulin plus a diet high in calories have mild diabetes Yet, if insulin is administered to such patients relatively large amounts are necessary to make much impression on the

units of insulin daily to correct a moderate hyperglycemia and yet when this large dosage of insulin is suddenly and completely withdrawn no acute manifestations result and indeed the blood sugar concentrations increase

but little (See Table 13, p 93) This is in contrast to the *underweight* diabetic patient who may be taking less than 100 units of insulin daily and who is sensitive to insulin, the sudden withdrawal of which would expose him to the risk of prompt and serious consequences From these clinical observations it is logical to conclude that pre diabetic obese persons maintain a normal blood sugar and delay or prevent the onset of diabetes by producing enormous amounts of endogenous insulin and that this increased demand leads eventually to an exhaustion of the islet cells and the onset of clinical diabetes in individuals also predisposed by heredity to this disease It appears unlikely that the explanation for these changes at this stage is to be found in a hormonal imbalance, although the initial onset of the metabolic abnormality may be so related Alterations in the total metabolism by a combination of reducing weight and a low caloric *intake on one hand and an increasing total body mass and* increasing weight on the other, offer a working clinical hypothesis which is merely a continued application of the principles laid down by Allen and which are applicable to the majority of adult diabetic patients when first seen by a physician for treatment

Seventy to 80 per cent of diabetic patients are, or give a history of having been, overweight, and yet in the reception room of a physician specializing in the treatment for diabetes there is no such predominance of the obese Many have lost weight prior to seeking help but have lost it in an undesirable manner, namely, from the progressiveness of the diabetes This results from loss of sugar and, at times, ketone bodies with no concomitant reduction in caloric intake Under these circumstances the insulin producing islet cells are subjected to a sustained stimulation to produce *maximum* amounts of insulin and the diabetes becomes intensified in direct proportion to the ensuing islet cell exhaustion

**Race.** All comprehensive studies of the racial incidence of diabetes show a higher frequency of this disease among Jewish males and females White and Pincus[7] contrast a positive family history of diabetes in 30 3 per cent of Jewish males with 23 per cent in all males, and 29 1 per cent in Jewish females with 26 5 per cent in all females Inbreeding tends by virtue of the predisposition by heredity to intensify this increased incidence of diabetes among Jews

**Endocrine Factors** Clinically, *the co existence of diabetes with other* endocrine disorders is not frequent However, its occurrence in patients with hyperfunctioning of the anterior pituitary and adrenal glands, as seen in Cushing s syndrome, and experimental studies leave no doubt concerning *endocrine* antagonisms Over 25 per cent of acromegalic patients develop diabetes

It is in the experimental field that most of our knowledge concerning disturbed harmony between the endocrine glands in diabetes has been

gained Permanent diabetes has been produced (1) by removal of the pancreas (Von Mering and Minkowski),[3] (2) by partial pancreatectomy—removing nine tenths of the gland—with subsequent overfeeding (Allen),[4] (3) by the injection of saline extracts of the anterior pituitary gland (Young),[5] (4) by the injection of alloxan [6] (5) by intraperitoneal injection of glucose in the cat (Dohan and Lukens) [7] Transient diabetes has been produced by injecting uric acid into glutathione deficient rabbits [8]

Allen proved the necessity of removing nine tenths of the pancreas before diabetes could be produced by overfeeding and his co workers, Copp and Barclay,[9] found that control of the diabetes prevented progressive degeneration of the islets of Langerhans and that hydropically degenerated cells in the diabetic animal could be rescued by controlling the diabetes with insulin and diet Lukens and co workers[10] who confirmed these observations believe that it is the hyperglycemia that is responsible for the degenerative changes in the islets These studies are of great importance to the physician treating diabetes They provide experimental support to the clinical conclusions of authorities in this field that control of the diabetes is an important force in preventing progression of degenerative changes in diabetic patients

When Young[5] produced permanent diabetes in dogs by injecting increasing amounts of an extract of the anterior pituitary gland he observed that a reduction in the number of islets resulted Haist[11] found a great reduction in the insulin content of the pancreas of animals made diabetic by Young's method Similarly, in the pancreas of the human diabetic Scott and Fisher[12] found that the average amount of insulin in the normal pancreas was 1 7 units per gram in contrast to the average of 0 4 units per gram in the diabetic A decreased production of insulin by the pancreas of the diabetic could explain the presence of diabetes in some cases But in the large number of patients who require much more insulin to control the diabetes than is produced by the normal pancreas, as judged by the insulin need of the depancreatized human other factors must be at work There may be profligate waste of insulin in the body in a manner not known This may be due to neutralization of insulin blocking of enzymatic processes destruction or inhibition by insulin antagonists or proteolytic enzymes any one or any combination of which may conceivably influence the onset of diabetes

**Miscellaneous Factors** *Age* The fact that the onset of diabetes is most frequent between the ages of forty five and sixty five has been presented as evidence in favor of a pituitary influence at an age when in women the concentration of the anterior pituitary hormone in the blood is high The onset of diabetes at puberty though with a much lower peak is considered to be due in part at least, to the increased production of the same hormone The onset of diabetes does not occur in direct rela

*but little* (*See Table 13, p 93*) *This* is in contrast to the underweight diabetic patient who may be taking less than 100 units of insulin daily and who is sensitive to insulin, the sudden withdrawal of which would expose him to the risk of prompt and serious consequences From these clinical observations it is logical to conclude that pre diabetic obese persons *maintain a normal blood sugar and delay or prevent the onset of* diabetes by producing enormous amounts of endogenous insulin and that this increased demand leads eventually to an exhaustion of the islet cells and the onset of clinical diabetes in individuals also predisposed by heredity to this disease It appears unlikely that the explanation for these changes at this stage is to be found in a *hormonal imbalance, although* the initial onset of the metabolic abnormality may be so related Alterations in the total metabolism by a combination of reducing weight and a low caloric intake on one hand and an increasing total body mass and increasing weight on the other, offer a working clinical hypothesis which is merely a continued application of the principles laid down by Allen and which are applicable to the majority of adult diabetic patients when first seen by a physician for treatment

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## SUMMARY

Those most likely to develop diabetes are of diabetic families are over weight are between forty five and sixty five years of age, and lead a sedentary existence

*Heredity* is the outstanding predisposing cause of diabetes It establishes the susceptibility to the disease according to a Mendelian pattern carrying recessive characteristics

*Obesity* from the clinical aspect is the most important precipitating cause of diabetes, occurring in 70 to 80 per cent of patients whose diabetes first becomes manifest in adult life Obesity, by virtue of an increased total metabolism makes the diabetic patient relatively resistant to insulin and it would appear that this same influence in the pre diabetic state and in the individual made susceptible to diabetes by heredity accounts for the exhaustion of the inadequate pancreas and the precipitation of clinical diabetes

Aging infections, arteriosclerosis, and trauma play little or no part in causing diabetes as it is generally known Hemochromatosis is a rare condition but one which causes diabetes


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tion to aging, the frequency of new cases decreasing steadily after the mid sixties

The tendency to become overweight in the forties and fifties with the resulting increase in total metabolism has a definite bearing on the increased incidence of new cases of diabetes at this age The decreasing total metabolism in later life has the opposite effect, probably accounting for the decline *in new cases after fifty five years of age*

*Infections* Infections play little, if any, part in causing diabetes Most infections, especially pyogenic infections, causing leukocytosis and fever, intensify the severity of diabetes while they persist It is not surprising therefore, that diabetes, undetected at other times, may be recognized for the first time during the course of such infections Viral infections and infections which do not cause leukocytosis, notably tuberculosis, have much less effect than pyogenic infections in increasing the severity of the diabetes during the course of the complication In fact, occasionally the progressive emaciation attending tuberculous infections has been noted to decrease *instead of increase the severity of the diabetes It would appear that the* decreasing total metabolism in such cases has a great insulin sparing effect which more than neutralizes the effect of the infection, and a decreasing insulin need ensues Infections involving the biliary and pancreatic tracts may conceivably cause secondary islet cell destruction with an ensuing diabetes If this does occur it must be rare The disturbing effects which infections exert on existing diabetes is dealt with in the chapter on complications

*Arteriosclerosis* Arteriosclerosis *per se* is not a cause of diabetes If it were, the incidence of this disease would not be decreasing during the phase of life in which arteriosclerosis is on the increase

*Trauma* Direct and extensive injury to the pancreas could conceivably cause diabetes, although this is extremely unlikely Injury to other parts of the body will not affect the carbohydrate function except through inactivity, fever, and changes in body weight that might result

*Destruction of the Pancreas* Progressive destruction of the islets by infiltrative lesions, tumors, by the fibrotic changes incident to hemochromatosis, *or secondary to pancreatic calculi, will cause diabetes* Such cases have no relation to the clinical problems of diabetes in general

*Endocrines* Hyperfunction of the pituitary and adrenal glands causes diabetes as seen in Cushing's syndrome, but the place of such glandular disorders in causing clinical diabetes as it is generally seen despite the fact that these disorders lend themselves well to laboratory study, is not clearly established Hyperfunction of the thyroid intensifies diabetes probably in a manner similar to obesity, namely, *in increasing the total metabolism* Cure of the thyrotoxicosis, like reduction of the obesity, usually ameliorates the diabetes

are they rare

A third group—the middle aged overweight patients—provide, not infrequently, candidates whose diabetes is pushed back and off the stage of detection by a reduction in weight through the agency of a reduced caloric intake The onset of the diabetes in these patients is not acute, the disappearance, *but not a cure*, of the diabetes is due to the reduced total body mass and hence the total metabolism by a means which spares islet cell function, and to the reduced need for insulin when the synthesis of fat from carbohydrate is reduced This is in contrast to the deleterious effect that accompanies the loss of weight due to the activity of the diabetes, features of which are hyperglycemia and the excretion of large quantities of sugar and acetone in the urine

The benefits of the reduction in weight by virtue of a restricted caloric intake form the basis of Allen s[3] undernutrition treatment Benefits from undernutrition are obtainable in the insulin era, in properly selected cases (see p 106) as we have previously demonstrated[4, 5, 1] Newburgh also has found support for the undernutrition regimen in the treatment of obese diabetic patients The diabetes is not cured by the reduction in weight by undernutrition means In spite of normal responses to glucose tolerance tests for varying periods a return of the former degree of obesity is invariably accompanied by evidences of diabetes Also, without a gain in weight diabetes puts in an appearance during the course of acute infections, notably pyogenic infections It would appear that in these cases the benefit is due to the reduction in total metabolism and that the supply of insulin insufficient for the obese state is adequate when the total body mass is reduced An analogy used in teaching patients is that a small furnace—in this case the pancreas—is incapable of heating a big factory or plant but if the size of the plant is reduced to conform with the size of the furnace satisfactory results ensue

It is clear that if the eradication of all signs of diabetes is to be achieved in the individual case, the diagnosis in the young diabetics must be made in the very early days of the disease and vigorous and adequate therapy must be employed, and that in the older overweight patients a suitable reduction in weight should be achieved in an appropriate manner and the ground thus gained must be held

**Prospects of Acquiring Complications** Diabetics are just as prone to develop most of the common diseases as are members of the general population They are more likely than their normal counterparts to be victims of certain *acute* disorders notably furuncles, carbuncles, tuberculosis and malnutrition, if their diabetes is uncontrolled

The prognosis will depend upon three integrated features (a) the

CHAPTER V

# Prognosis

The prognosis or outlook for the diabetic patient should be evaluated from (a) the standpoint of *a possible cure* of the diabetes and the advantages of *good control* of the disorder in its chronic form, (b) the prospects of *acquiring complications* with the influences that play for or against their development, and (c) *life expectancy*.

**Possibilities of Curing Diabetes.** A cure cannot be promised in any case of diabetes Yet, those who have seen many of these patients have encountered occasionally one whose diabetes apparently disappears following appropriate treatment At least, the diabetes is no longer detectable using the usual diagnostic measures This is an unusual occurrence and one that should not be looked upon as a cure until many years pass with normal responses to annual diagnostic tests One of us has had a special interest in two children followed for many years after all detectable signs of an acute diabetes had disappeared In both cases the onset was acute In one it was possible to record the onset of symptoms to a certain afternoon It is highly probable that in such cases acute reversible processes are taking place in the islets of Langerhans and that prompt and adequate treatment rescues a number of "knocked out" functioning units sufficient to produce insulin in amounts adequate to erase evidences of diabetes

Allen and his associates[1] have demonstrated that, in animals islet cells in a state of hydropic degeneration can be redeemed by relieving the functional overstrain on these cells by restoring to and maintaining the blood sugar at normal concentrations by means of diet and insulin Lukens and Dohan[2] have confirmed these observations

Illustrative of the transient disappearance of diabetes is the case of J E., aged thirty-eight years height 6 feet weight 180 pounds who while en route to the [illegible] thirst and polyuria Treated [illegible] venous) sugar [illegible] units of pro[illegible]rovement was [illegible] subjected to a glucose tolerance test on May [illegible] 1940 in [illegible] necessary for him to secure a pension The fasting blood (venous) sugar value was 119 mg per 100 cc and values after taking 100 gm of glucose were one half hour 137 mg one hour 88 mg two hours 96 mg and three hours 93 mg Subsequent tests

of therapy vary greatly Those we have set, and our aims, are outlined in Chapter XIII Life insurance policies are issued to selected diabetic patients who are known to be conservative and cooperative

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change in the character of the diabetes as a result of the complications, (b) the management of the complication and (c) the proper evaluation of and the institution of appropriate measures to combat the influence which diabetes has upon the complication and vice versa These features are dealt with in Chapters XV to XVII Actually, when suitable treatment is available the outlook for the diabetic suffering from most of the acute complications is excellent It is as good as in the nondiabetic Diabetic coma, the specific acute complication of diabetes, has become an uncommon cause of death—less than 2 per cent of diabetic deaths in well equipped hospitals

The complications which cause most concern are those characterized by *chronic degenerative changes*—vascular disease, notably disease of the coronary arteries and of the arteries of the extremities, diabetic retinitis, intercapillary glomerulosclerosis and the diabetic neuropathies

Disease of the coronary arteries is the most common cause of death in diabetics at the Pennsylvania Hospital, accounting for 18 deaths in 514 diabetic patients admitted to the public wards because of acute complications Malignant tumors was the second most common cause of death, occurring in 9 of the 514 patients, and cerebral vascular accidents the third in frequency, accounting for 8 deaths Intercapillary glomerulosclerosis is a menace of increasing proportions (see p 197) In fact, it was the most common cause of death in patients whose diabetes developed in childhood and who had survived fifteen or more years,[8] whereas deaths from diabetic gangrene have declined precipitously since the advent of extensive antibiotic therapy

*Evidence is steadily accumulating* that the likelihood of the diabetic acquiring any or all of these distressing chronic complications increases with the duration of the diabetes and the increase bears a direct relation to poor control of the diabetes

***Life Expectancy.*** *The normal life expectancy for white males and* females in the United States, as calculated in 1946, was 65 1 and 70 3 years, respectively Statistics issued by the Metropolitan Life Insurance Company[9] indicate that the life expectancy for white male diabetics is 62 12 and for white females, 66 20 years *The proximity of the life expectancy* for diabetic patients to the normal expectancy has progressed rapidly since the discovery of insulin Actually, many diabetic patients outlive the normal life expectancy

The child diabetic lived *but a short time—a scant two years—in the* pre-insulin era Contrast this with Joslin's[10] statistics of today—of 2659 diabetic children treated since 1898, 2235 are alive!

The prognosis for the intelligent and cooperative diabetic patient is excellent if the diabetes is identified early *and treated diligently by a physi*cian who has interest and training in this field of metabolism Standards

the injection The degree of effect and duration of action are reduced or intensified by decreasing or increasing the doses, respectively There is no need to give insulin intravenously except in doing insulin tolerance tests and part of the initial dose in the treatment of a patient in diabetic coma is given in this manner (see p 231) The effect of insulin on the blood sugar level may be masked by frequent and liberal intake of food, particularly carbohydrate and, as would be expected, the effect is more apparent when no food is given

Insulin is a protein and as such is destroyed by gastric juices, hence it is ineffective when given *by mouth* The hypoglycemic effect which follows the injection of insulin is due to an *increased rate of withdrawal of sugar from the blood by body tissues* Insulin permits *increased deposits of glycogen in skeletal muscles, providing hypoglycemic levels are prevented Glycogen is also deposited in greater quantities in the liver of the diabetic patient when the diabetes is controlled by treatment with insulin* Insulin administered to normal animals causes a reduction in the hepatic glycogen *In the diabetic insulin also exerts an antiketogenic effect it increases the respiratory quotient, it reduces the concentration of serum inorganic phosphate and serum potassium, and it inhibits protein catabolism when administered to the diabetic patient who is excreting large amounts of sugar and ketones*

Lack of insulin results in a reduction in utilization and in a shortage of carbohydrate in the peripheral tissues Insulin promotes utilization of glucose—complete oxidation, or deposition as glycogen, or synthesis to fat —by effecting a control over an enzyme, hexokinase (Cori) This enzyme exerts a catalytic action on the metabolism of glucose with adenosine triphosphate (ATP) to produce glucose 6 phosphate—a product available for oxidation, or for conversion to glycogen, or for synthesis to fat—a basic phosphorylation process These processes studied *in vitro* were found to result when insulin completely released the inhibition of the hexokinase by pituitary and adrenal cortex fractions

"The fall in the blood sugar level is a direct reflection of the influence of insulin on the basic phosphorylation, in so far as it causes a greater rate of removal of sugar from the blood (Soskin) [3] Insulin also participates in reactions in the tricarboxylic cycle[4]—in the specific synthesis of phosphate in the metabolism of pyruvate to carbon dioxide and in accelerating the conversion of acetate to fatty acids Though investigators have gained headway in solving the problems surrounding the action of insulin much is still not clear.

The fact that insulin is not essential for glycogen to be restored to skeletal muscles following physical exercise is of considerable clinical significance The rate but not the extent of restoration is reduced if insulin is absent (Lukens) [5] In the insulin treated patients the withdrawal of sugar from the blood for the replenishment of glycogen in muscles is an impor

CHAPTER VI

# Insulin

**Discovery of Insulin.** '*On the 27th of July, 1921*, we had a depancreatized dog and we decided to begin treatment. A duct tied dog was *chloroformed and the degenerated* residue of pancreas was removed. *It* was chopped into small pieces in a chilled mortar and frozen in brine. The mass was *ground up and about 100 cc of saline added. Of this* extract 5 cc were administered intravenously into the depancreatized dog. Samples of blood were taken at half hour *intervals and showed that the blood sugar* had fallen from 0.20 to 0.11 per cent in two hours. The clinical condition of the dog was remarkably improved' (Banting)[1] An *effective* blood sugar lowering agent was thus discovered. At first it was called "isletin" but Macleod in whose laboratory Banting worked, indicated that the new product would be *insulin* and shortly, through the cooperative enterprise of the Connaught Laboratories of Toronto and the Eli Lilly Company of Indianapolis this preparation, now designated as regular or unmodified insulin, was being used widely in the treatment for diabetes.

Insulin is protein in nature and is standardized in units. A *unit* is the amount of the crystalline preparation required to reduce the blood sugar level of a normal fasting (twenty four hours) rabbit weighing 2 kg from normal (120 mg per 100 cc) to 45 mg per 100 cc within five hours.

The clear aqueous solution of insulin hydrochloride known as *regular insulin* was the only insulin available from 1922 until the discovery of protamine insulin *by Hagedorn of Copenhagen, Denmark, in 1936*.

**Regular Insulin.** Regular insulin—a clear solution—when administered *subcutaneously has a blood sugar lowering effect which is* perceptible within one hour, with its greatest effect between three and six *hours, after which the effect* wears off—usually about seven to ten hours after the injection is given (Fig 3). The hypoglycemic effect is greater and more prolonged when large doses are given than when the amounts injected are small.

When administered *intravenously* regular insulin exerts a perceptible reduction of the blood sugar within a few minutes with greatest effect in twenty to forty five minutes, following which the pre injection blood sugar concentrations are usually restored between one and two hours following

acterizes the regular insulin These two insulins lend themselves well to a method of combined therapy—one dose of protamine zinc insulin for its slow but long action and one dose of regular insulin given for action at a time when the protamine zinc insulin is least active and at a time when a prompt but short effect is desired In the majority of cases this will be in the morning when the effect of the previous day's dose of protamine zinc insulin is on the wane, when the present day's dose of protamine zinc insulin, by virtue of its retarded effect, is not well "under way," and when quicker action than is possible from protamine zinc insulin is needed to prevent a marked hyperglycemia after breakfast and, indeed, after lunch This combination of protamine zinc insulin and regular insulin is widely used The practicability of mixing the two insulins is considered on page 145 Mixtures, when suitably effective, are very welcome, as they reduce the number of injections needed However, the number of diabetics who have as good results with the mixture as with the two insulins injected separately is disappointingly small

It may be added here that the slowness of the action of protamine zinc insulin makes it a poor agent to cope with sudden or rapidly varying demands Hence alone it is not a satisfactory form of insulin therapy during the course of acute complications (see p 215) Also, the number of patients in whom good control of the diabetes is possible with this insulin alone is small Usually if the twenty four hour insulin need is in excess of 18 or 20 units, additional rapidly acting insulin is indicated The protamine zinc insulin is supplemented usually by one and rarely by two other doses of regular insulin or by one dose of globin insulin for most uniform results (see p 143)

In the event of overdosage—the protamine zinc insulin being administered before breakfast—the hypoglycemic reaction is most likely to occur between three o'clock in the morning and breakfast time This is what would be expected—at the end of the longest period in the twenty four hours without food and with an insulin which is effective for over twenty four hours

Protamine zinc insulin has reduced the number of injections necessary, it has permitted measuring instead of weighing diets in all but the exceptional cases, it has made more uniform the control of the diabetes than was possible formerly, it reduces the degree of oscillation of blood sugar values and with it there is less glycosuria and fewer cases of coma and of tuberculosis in diabetic patients than occurred formerly

**Globin Insulin.** Globin insulin—a clear insulin—was made available commercially in 1942 (Reiner, Searle and Lang) [8] It has all the general properties of insulin but with a blood sugar lowering action which is intermediate between regular insulin and that of protamine zinc insulin Globin insulin reduces the blood sugar more slowly but for a longer time than does regular insulin and its effect is more rapid than, but not as pro

tant cause of hypoglycemia after extra physical exercise This feature contributes to the instability of the blood sugar concentration in children particularly

The discovery of insulin led to increased diet allowances for the diabetic but the shortness of the blood sugar lowering effect and rapidity of action of regular insulin (Fig 3) necessitated multiple doses in most cases when insulin was needed Many patients needed four injections of insulin per day to control adequately the diabetes

Crystalline insulin (zinc insulin crystals in solution) exerts effects indistinguishable, clinically from those of regular insulin[6] Crystalline insulin is available on the market though its production has been greatly

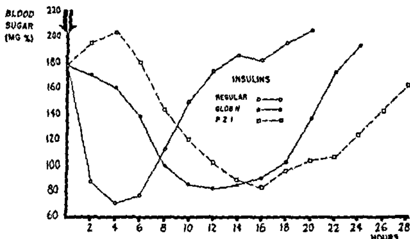



*Fig. 3* The comparative effects of identical doses—60 units—of regular globin and protamine zinc insulin when administered subcutaneously to a hyperglycemic patient who received 20 gm of carbohydrate by mouth at two hour intervals during the observations

curtailed owing, in part, at least, to a loss of units during manufacture It is interchangeable clinically with an equal number of units of unmodified insulin

**Protamine Zinc Insulin.** This product a *cloudy amorphous insulin* suspension available as the result of Hagedorn's[7] discovery (1936) and the part played by Scott and Fisher[8] in adding zinc to protamine insulin, carried advantages which, when combined with those of regular insulin, improved greatly the lot of the diabetic patient Protamine zinc insulin is slowly absorbed following subcutaneous injection—*it is never given intravenously*—and exerts a correspondingly retarded insulin effect Also *this effect is prolonged—twenty four to thirty six hours following the injection* (Fig 3) This more prolonged and more uniform effect of protamine zinc insulin, reducing the extent of the oscillations of the blood sugar concentration, is in contrast to the rapid action of short duration which char

the total were given as protamine zinc insulin But, a 2 1 or a 3 1 mixture, with regular insulin considerably in excess of that with which the excess protamine could combine, exerts a rapid as well as a prolonged action

NPH insulin has a more rapid effect in reducing the blood sugar than has protamine zinc insulin and a slower effect than that of regular insulin The initial influence on the blood sugar is almost identical with that of globin insulin which is illustrated in Figure 3

The duration of the blood sugar lowering effect of NPH insulin is somewhat shorter than that of protamine zinc insulin This effect is considerably longer than that of regular insulin and somewhat longer than that of globin insulin In the event of overdosage—the insulin being administered before breakfast—hypoglycemic reactions are most likely to occur in the late afternoon, in the evening, or during the night NPH insulin is, therefore, an insulin with an intermediate action and a product which lends itself most advantageously to mixing with regular insulin

It would appear from three years experience with this insulin, that a combination of NPH with regular insulin in proportion of 4 1 would permit satisfactory control of diabetes with one injection daily in a much larger number of patients than is possible with any one of the three insulins in general use The regular insulin would serve to prevent the tendency to hyperglycemia during the forenoon and thereafter for the remainder of the twenty four hours the action of the NPH insulin would be adequate in most cases to maintain satisfactory blood sugar values Regular insulin tends to combine with NPH insulin if they are allowed to stand for long periods after being mixed Hence, mixing at the time of injection is desirable

**Other Insulins.** Many insulins have been tried in the search for the perfect product which would become available after injection only when it was needed In other words, the perfect insulin should be under a control similar to that exemplified by a normal pancreas Attempts to secure such an insulin are not to be discouraged but in the meantime we must strive for the greatest advantages that can be secured with the insulins already at hand

**Absorption of and Sensitivity to Insulin** The injection of radioactive insulin and the detection of the rate of disappearance of the injected material confirmed what formerly has been assumed, i e, the regular insulin is absorbed and disappears most rapidly Next to disappear is the globin and the slowest to be absorbed is the protamine zinc insulin (Reiner).[12]

The rate of absorption of insulin is reduced in some cases of idiopathic insulin resistance and when insulin is injected into indurated areas The rate of absorption in most cases determines the speed and duration of action This is not always the case, however In a very important group of diabetics—important chiefly because of their numerical strength—namely,

longed as, that of protamine zinc insulin (*Fig 3*). *Globin insulin has* earned a secure place in the treatment for diabetes[10] Wisely used in properly selected cases globin insulin, like each of the other insulins and combinations of insulins, has its sphere in which it is the insulin of choice Unsatisfactory results with globin insulin indicate improper selection of the patient *for this type of therapy or improper distribution of the diet* or timing of the administration of the insulin The selection of appropriate patients for their respective insulin treatments is dealt with on pages 139 to 149 Globin insulin shares, to some degree, some of the advantages of protamine zinc insulin but the specific indications for its use are when a *maximum permissible* dose of protamine zinc insulin *fails to act quickly* enough to avoid heavy reactions for glycosuria in the forenoon and yet if the dose were increased hypoglycemic reactions would occur in the early morning In a considerable number of such cases a single daily dose of globin insulin will eliminate the necessity of a supplementary dose of regular insulin Similarly, a dose of globin with protamine zinc insulin (not mixed) will on some occasions avoid the necessity of an injection of insulin before supper (see p 146)

Globin insulin injected subcutaneously causes a detectible reduction of the blood sugar within two hours reaching its greatest effect between six and twelve hours, with the effect subsiding from sixteen to twenty four hours (Fig 3) These effects are intensified when large doses are given—*there is a more prompt effect, a greater hypoglycemic effect and one of* longer duration When used in therapy globin insulin is administered preferably one hour before breakfast and in the event of overdosage the hypoglycemic reaction is most likely to occur between 3 o'clock in the afternoon and suppertime Patients tend to prefer the risk of a hypoglycemia *during the daytime rather than in the early morning hours*, *as occurs in* the case of an overdose of protamine zinc insulin

**NPH Insulin.** A new and modified protamine zinc insulin—NPH insulin—though a relatively new preparation gives promise of earning an important place in the clinical control of diabetes This insulin was prepared by a method developed in *Hagedorn's laboratory by Krayenbuhl and Rosenberg*[11] NPH insulin, until recently referred to as NPH 50 insulin, is administered as a cloudy suspension of a crystalline precipitate and contains only 0 50 mg of protamine per 100 units in contrast to 1 25 mg per 100 units of the protamine zinc insulin in general use The greatest value of this new insulin lies, in our experience, in *the fact that additions of regular insulin* can be made to it without sacrificing much of the rapid action *of the regular insulin* In contrast, when regular insulin is added to protamine zinc insulin—containing 1 25 mg of protamine per 100 units—the regular insulin combines with the excess protamine until the ratio of the units of regular insulin to those of protamine zinc insulin exceeds 1 1 In other words, a 1 1 mixture may be expected to act the same as though

duces the serum phosphorus concentration and inhibits protein catabolism

Insulin, it is believed exerts control over an enzyme hexokinase which in turn exerts a catalytic action on the metabolism of glucose with adenosine triphosphate to produce glucose 6-phosphate—a process which is essential before the products of insulin action mentioned above are possible Insulin exerts an influence in at least three phases of the tricarboxylic cycle

Insulin is rendered ineffective when given by mouth

The middle aged obese diabetic patient is relatively insensitive to insulin The sensitivity to insulin is increased with appropriate reduction in body weight

Clinical observations of sensitivity to insulin are still superior to special tests

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the overweight diabetics, usually of middle age, insulin is relatively in effective (see p 93) This, we believe, is on the basis of an increased *total metabolism* Certainly, if their weights are reduced these patients become increasingly sensitive to insulin and if their lost weight is regained so also is the relative insulin insensitivity It is fully realized that this explanation is not complete but for practical clinical purposes it suffices until further discoveries show means for improved application in therapy

Special tests for insulin sensitivity are surrounded by a multitude of modifying influences which may add to the confusion and, if not considered, the bland acceptance of the result as being meaningful is prone to mislead

The lack of widespread adoption of insulin tolerance tests is evidence against their clinical value To interpret the result properly, quantitative hormone studies on urine and serum are necessary in addition to appropriate consideration of the diet combinations preceding the test as well as complicating disorders that might alter the results, not all of which are measurable

A *modified Radislav test, which shows the differences occurring between* venous and capillary blood sugar concentrations four to five hours following the injection of insulin, is said to detect the source of insulin *resistance, be it hepatic in origin or in the peripheral tissues*

Himsworth s test of insulin sensitivity comprises the administration of insulin by vein and glucose by mouth simultaneously and observing the effect on the capillary blood sugar at short intervals for one and one half hours The patient is considered insulin sensitive if the expected rise of the level of the capillary blood sugar is prevented by the insulin and insulin insensitive if the capillary blood sugar values increased as though little or no insulin had been given The lack of uniformity of results has prevented this test being of clinical value in general

It would seem highly probable that these tests are measures of hepatic responses and that the lack of uniformity results from the fact that the influences on liver functions are legion This is in keeping with the views of Soskin and Levine [13]

## SUMMARY

Insulin was discovered by Banting and Best in 1921 It is available in *four forms* *Regular insulin* with rapid action of short duration, approximately six to eight hours *Globin insulin*, with a slower and longer action sixteen to twenty four hours *Protamine zinc insulin*, which goes into action slowly but exerts a blood sugar lowering effect for twenty four to *thirty six hours* and the fourth insulin—*NPH insulin*—with an intermediate effect

Insulin used clinically lowers the blood sugar, reduces glycosuria in *the diabetic and* increases the deposits of glycogen in the muscles and liver It exerts an antiketogenic effect raises the respiratory quotient re

duces the serum phosphorus concentration and inhibits protein catabolism

Insulin it is believed exerts control over an enzyme hexokinase which in turn exerts a catalytic action on the metabolism of glucose with adenosine triphosphate to produce glucose 6-phosphate—a process which is essential before the products of insulin action mentioned above are possible Insulin exerts an influence in at least three phases of the tricarboxylic cycle

Insulin is rendered ineffective when given by mouth

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Clinical observations of sensitivity to insulin are still superior to special tests

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CHAPTER VII

# Carbohydrate Metabolism and the Blood Sugar

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**Introduction.** Custom, arising from early investigative work, has led physicians to consider diabetes a disorder primarily of carbohydrate metabolism Gross changes in the metabolism of carbohydrate certainly accompany the changes which characterize this disease However, with means available to investigate pure rates of synthesis and degradation of body constituents, it is clear that there is a fundamental metabolic pool[1] in which the products of carbohydrate protein and fat mingle and that *hypo insulinism (diabetes) is characterized by a reduction in fatty acid synthesis, a decreased glycogen production and, in the more severe states, accelerated protein breakdown* It is clear too from the clinical standpoint that carbohydrate is but one of the important dietary factors to be considered In fact, the total caloric intake when reduced has a more profound ultimate effect in controlling the diabetes than have reductions in the carbohydrate intake unless the total calories are reduced also[2] A maximum effect in reducing the need for insulin might be expected when both carbohydrate and total calories are reduced and when physical activity is a prominent feature This is exactly what occurs, and in treating the obese diabetic both dietary restrictions are permissible, exercise is encouraged and, in such cases, these features provide, short of insulin therapy, the most powerful means of controlling diabetes

Carbohydrate is more prompt in its effect on the diabetic state, whether added or reduced than are changes in protein, fat or total caloric intakes Carbohydrate is indispensable and is the most readily available food for energy purposes It affects the level of the blood sugar immediately upon its absorption Because of the promptness of the effect of carbohydrate on the yardstick by which we determine the control of diabetes—referring to the blood sugar level—it is appropriate to deal with carbohydrate metabolism and the blood sugar in some detail

### CARBOHYDRATE—SOURCE, DIGESTION, ABSORPTION

**Source.** In the normal diet the chief sources of carbohydrates are cereals (including grain products), vegetables, fruits syrups, and sugars Ordinarily, the sugars and syrups are not included in the diabetic's diet,

the reasons being that, with some restriction in the total carbohydrate intake it is preferable that concentrated forms be avoided, permitting liberal helpings of fruits and vegetables which carry the added advantages of providing minerals and vitamins It is estimated that 58 per cent of protein foods, and 10 per cent of fatty foods, are available in metabolism as carbohydrate Hence, the theoretical glucose equivalent (G E) of a diet is

Carbohydrate + 0 58 protein + 0 10 fat

**Digestion.** Carbohydrate foods on ingestion are subjected, while still in the oral cavity, to the action of ptyalin—secreted by the salivary glands—which on mixing with the foods, initiates the conversion of starch to maltose, and glycogen to dextrose This process is continued in the stomach until the salivary amylase activity is stopped and acid hydrolysis substituted when the hydrochloric acid becomes mixed with the food The digestion is continued in the alkaline medium of the small intestine by the pancreatic amylase and the intracellular enzymes—amylase, invertase and lactase—after the passage of the sugars into the cells of the intestinal mucosa By selective actions these enzymes reduce the sugars to monosaccharides (chiefly to glucose but also to fructose and galactose) the state in which they are absorbed into the blood

**Absorption.** It is of clinical importance, especially in dealing with hypoglycemic patients, that sugar is not absorbed in significant amounts from the stomach unless in the form of glucose and this in concentrations over 40 per cent Hence functional or organic pyloric obstruction might prevent the correction of a hypoglycemic reaction by carbohydrate administered orally in dilute forms Syrups, such as Blue Label Karo Syrup, because of their high concentrations of absorbable sugars are more likely to correct a hypoglycemia in event of delayed emptying of the stomach than are fruit juices which must reach the small intestine to be absorbed It is noteworthy on the other hand that sugar to be absorbed by the small intestine must be reduced to isotonic concentrations [3] It would appear that in the absence of delayed gastric emptying time, the weaker solutions, such as orange juice, would correct a hypoglycemia more readily than would 40 per cent sugar solutions Maximum absorption of sugars takes place in the small intestine Absorption of glucose occurs in the colon in hypoglycemic individuals but not, to a significant degree, in normal subjects

Absorption from the small intestine involves (a) a phosphorylation process, a specific process rapidly accomplished through the combining of the sugar with the phosphate in the intestinal wall, and (b) simple diffusion, a slower and nonspecific process

The rate at which dietary sugars reach the blood is influenced by the speed of arrival of food in the intestine, the concentration of sugar, the

*mixture of foods* (complex mixtures delay absorption) and the available phosphorylating capacity The quantitative absorption of sugar involves the state of the intestinal mucosa, the duration of exposure of sugar to the absorbing surface endocrine influences (excessive thyroid activity accelerates the rate of absorption and vice versa, pituitary and adrenal cortical *deficiency reduce absorption) and the adequacy of the* vitamin intake

Infections, deficient intake of B complex, and inanition inhibit the absorption of sugars Insulin, apparently, has no effect on the absorption of sugar from the intestine

Carbohydrate, once absorbed into the blood, is available, according to the priority existing at the time, for (a) *energy purposes with complete* oxidation, (b) storage as glycogen in the liver and in the muscles, (c) conversion to fat and (d) distribution in the body fluids—notably the blood—in concentrations which, under normal conditions, remain remarkably constant The last mentioned is the supply line to all tissues

Carbohydrate, in addition to its use as fuel, has a protective and detoxifying effect in the liver It spares protein metabolism and has a far reaching effect on the regulation of the metabolism of fat Fatty acids are partially *metabolized in the liver but their complete oxidation takes place in the* peripheral tissues Ordinarily the amount of fatty acids in transport is small and no detectable amounts of acetone, diacetic acid or beta oxybutyric acids—using usual tests—are present in the blood or urine However, if the fatty acid breakdown is accelerated as occurs in uncontrolled *diabetes accompanying reduced carbohydrate stores and reduced carbohy*drate metabolism, ketone bodies appear in the urine and finally, barring relief, they accumulate in the blood This state is known as ketosis and in the extreme degree will cause coma—*diabetic coma*

## REGULATION OF THE BLOOD SUGAR LEVEL

The constancy of the level of the blood sugar between fixed, but not widely separated, extremes of normal is an ideal example of homeostasis The stability of the *blood sugar is the more remarkable in view of the mul*titude of factors which influence the amounts of glucose which enter the blood and the amounts that are withdrawn The wide range of the adaptability of the homeostatic mechanism is appreciated when it is known that glucose can be administered intravenously at the rate of 0 80 gm per *kilogram of body weight* per hour and that the rate of administration can be materially increased after one or two hours without causing glycosuria (Wood, Gatt, 1915, and Jordan, 1927)

The concentration of glucose in the blood at any one time *represents the* equilibrium between the contributing and extracting mechanisms which when upset by disease, may permit hyperglycemia as in diabetes or hypoglycemia, as in adrenal cortical insufficiency or hyperinsulinism Conditions which tend to affect the rate of glucose exchange to and from the

blood are listed in Table 7 The quantity of carbohydrate ingested, insulin and physical exercise are especially important daily considerations in the management of diabetes These will be discussed elsewhere under their respective headings

The concentration of the blood (venous) sugar, under normal conditions, remains relatively constant—70 to 110 mg per 100 cc in the fasting and 90 to 160 mg in the postprandial states—with the "giving and taking

TABLE 7

Factors Influencing the Level of the Blood Sugar

| HYPOGLYCEMIC | HYPERGLYCEMIC |
|---|---|
| *Diet* | |
| Prolonged undernutrition | Excessive carbohydrate intake |
| Decreased rate of absorption of glucose e g , pyloric obstruction | Increased rapidity of absorption of glucose e g gastro-enterostomy |
| *Physical Exercise* | |
| Increased exercise | Reduced exercise in diabetic subjects |
| *Liver* | |
| Hepatocellular damage (certain cases) | Hepatocellular damage (certain cases) |
| *Kidney* | |
| Renal glycosuria as in nephrosis | |
| *Hormones* | |
| Anterior pituitary deficiency | Acromegaly |
| Hypothyroidism | Pituitary basophilism |
| Hyperinsulinism | Hyperthyroidism |
| Adrenal insufficiency (cortical) | Pheochromocytoma some cases |
| Panhypopituitarism | *Diabetes mellitus* |
| *Medications* | |
| Insulin | Epinephrine |
| | Anesthesia |
| | 17 hydroxycorticosterone (Compound F) |
| | 11 dehydro-17 hydroxycorticosterone (Compound E—cortisone) |
| *Functional Nervous Disorders* | |
| Anorexia nervosa and other anxiety states | Toxemias |
| Neurocirculatory asthenia | Fright |
| | Trauma—intracranial |
| | Anger |

mechanisms' at work Minute changes in the blood sugar concentration accelerate or depress the rate of release of glucose from the liver Soskin has shown that glucose administration by vein not only halts the outflow of sugar from the liver but is followed by marked increase in the uptake of sugar by this organ This is followed by a period during which no sugar is taken up nor excreted by the liver and as the sugar content of the arterial blood decreases below its original value the liver resumes its out

put of sugar This thermostat like regulation of the blood sugar is pro *foundly upset* when the supply of insulin is inadequate, as occurs in diabetes

The blood sugar level is lowest in the fasting state A mixed diet— protein, fat and carbohydrate—raises the concentration of sugar to a less degree than a meal containing a large proportion of carbohydrate If the carbohydrate is in a readily absorbable form such as dextrose, fruit juices and syrups, the blood sugar is affected more rapidly and usually to a more marked degree than by a mixed meal or even a meal high in starch Pro tein has a minimal and fat a negligible effect on the blood sugar con centration in the postprandial phase

Conditions which permit carbohydrate to reach the small intestine rapidly, as in cases of gastro enterostomy, and which speed the rate of absorption of glucose, as occurs in hyperthyroidism, account for an un usually rapid elevation of the blood sugar and also a degree of hypergly cemia greater than would occur in the normal individual

## THE BLOOD SUGAR IN DIABETES

Abnormally high blood sugar concentrations are essential to the diag nosis of diabetes A concentration of sugar in excess of 130 mg per 100 cc in a specimen of venous blood taken after an eight to fourteen hour fast is usually due to diabetes, as are values in excess of 170 mg per 100 cc in blood samples taken after meals In *extremely mild* diabetes fasting and *postprandial* blood sugars may be normal and only by means of special tests (see p 77) can the disease be detected If diabetes is present even to this mild degree, acute febrile complications usually make it manifest by causing hyperglycemia and glycosuria

In *mild* untreated diabetes the fasting blood sugar may be normal in amount or it may exceed 130 mg per 100 cc but in these cases values higher than normal—in excess of 170 mg per 100 cc —usually prevail after meals

In *moderately severe* diabetes higher blood sugar concentrations are encountered—250 to 350 mg per 100 cc are not unusual

In *diabetic coma,* values between 300 and 800 mg per 100 cc are com mon Occasionally extremely high values are encountered such as in the case of E D (p 236), whose blood sugar amounted to 1150 mg per 100 cc

There is practically no difference in the sugar concentration in venous and arterial (capillary) blood in the fasting state After a meal, however, in the normal person the arterial blood sugar level is from 20 to 50 mg per 100 cc higher than that in venous blood *This difference between* venous and arterial blood sugar concentrations is an indication of the quantity of sugar withdrawn from the blood to be oxidized, converted to

fat or stored as glycogen As might be expected this difference is less in untreated and uncontrolled diabetes

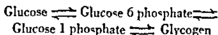
The magnitude of the fluctuations in the concentration of sugar in arterial blood far exceed those observed in venous blood Also, the incidence and degree of error is usually greater when capillary blood is used for blood sugar determinations For clinical purposes we prefer venous blood sugar determinations probably because it is with this method that we have had most experience The practice of using venous blood for this purpose is almost universal in America and the method most widely used in determining blood sugar values is that of Folin and Wu whereas capillary blood is the more widely used in Europe and the methods employed for quantitative sugar analyses are those of Bang Hagedorn and Jensen and McLean Blood sugar values by the Folin and Wu method include nonglucose reduction fractions—glutathione cysteine ergothionine creatinine and others as yet unidentified which have been considered to be rather constant and which account for 10 to 30 mg per 100 cc However Mosenthal[4] reports that these nonglucose reducing substances exceeded the upper limit of 30 mg per 100 cc in a considerable proportion (38 per cent) of 200 consecutive cases studied and as a result advocates that the true glucose values be determined He recommends the micro method of Lauber and Mattice[5] for this purpose

In the usual management of diabetes and even in most diagnostic studies experience has shown the macro method of determining the blood sugar (true blood sugar plus other reducing substances) to be satisfactory However in borderline cases unusually high concentrations of nonglucose substances might tip the scales toward an unjustified diagnosis of diabetes In such cases true glucose values would be special importance The other alternative and the one we have used is to do a series of tests using the macro method of determining the venous blood sugar values before making a definite decision

The major sources of glycogen are preformed carbohydrates—sugars and starches—and proteins of the diet Glycogen is formed during fasting states from noncarbohydrate sources by the liver This process is *gluconeogenesis* This is an important source of sugar during fasting in the normal and one that is drawn upon heavily in uncontrolled diabetes Also gluconeogenesis is affected by adrenal cortical hormones removal of which reduces tissue protein breakdown Conversely the injection of an excess of these hormones increases the rate of protein breakdown making available glucose from the metabolism of the resulting amino acids

Carbohydrate is the chief source of energy in the body Energy is liberated throughout the dissimilation of carbohydrate by means of certain phosphorylation processes the completion of which depends upon enzymatic activity a long period of which takes place in the conversion of gly

cogen to pyruvic acid,* and finally to $CO_2$ and water In the event of relative anoxia, some of the pyruvic acid is reduced to lactic acid which is restored to the economy of the body (see below) Pyruvic acid is also an excellent glycogen former (Long) The *formation of glycogen* is dependent on the following reactions *Glucose* plus *adenosine triphosphate* in the presence of the essential and active, uninhibited enzyme *hexokinase*, yields *glucose 6 phosphate* and *adenosine diphosphate* Glucose 6 phosphate upon transphosphorylation yields glucose-1 phosphate which combined with phosphorylase activity yields glycogen as follows



$$\text{Glucose} \rightleftharpoons \text{Glucose 6 phosphate} \rightleftharpoons$$
$$\text{Glucose 1 phosphate} \rightleftharpoons \text{Glycogen}$$

It is significant that experimentally the hexokinase activity—essential *for the production of glycogen from glucose*—can be inhibited by injecting anterior pituitary extract and that this inhibition may be neutralized by administering insulin [6]

The mechanisms involved in *glycogen breakdown* to $CO_2$ and water proceed anaerobically to the pyruvic acid stage at which point adequate oxygen is needed to complete the metabolism to $CO_2$ and water Lacking adequate oxygen, pyruvic acid is transformed to lactic acid which is reconverted, by the liver, into glycogen Clinically, this is of some importance as it explains a means by which a hypoglycemic individual in convulsions can tap the muscle glycogen in the effort to correct the hypoglycemia Convulsions and the rapidly ensuing increased formation of lactic acid, which is rapidly converted to glycogen which in turn is a ready source of sugar, have doubtless saved the lives of some diabetic patients who have weathered severe hypoglycemic reactions, unassisted, to spontaneous recovery

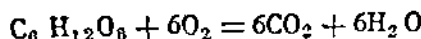
## RESPIRATORY QUOTIENT

*(and the relative combustion rates of protein, fat and carbohydrate)*

Clinically, consideration of the respiratory quotient is of little moment but as it is altered in diabetes it should be understood by students of this subject The respiratory quotient (R Q) is the ratio of the volume of carbon dioxide produced to the volume of oxygen absorbed by a tissue

$$\text{R Q} = \frac{\text{Vol } CO_2 \text{ produced}}{\text{Vol } O_2 \text{ absorbed}}$$

In the metabolism of glucose no call for oxygen beyond that already in the food is necessary for the oxidation of the hydrogen as shown in the equation



$$C_6H_{12}O_6 + 6O_2 = 6CO_2 + 6H_2O$$



and for each molecule of $O_2$ absorbed a molecule of $CO_2$ is formed Hence, if carbohydrate only is being metabolized, the R Q is 1 0 During the metabolism of fat alone the quotient is 0 71, for protein it is 0 80, for alcohol it is 0 67 and on an ordinary mixed diet the R Q is about 0 85 The quotient is taken as an indication of the type of food being metabolized —the closer to 1 0 the higher is the percentage of carbohydrate and the closer to 0 7 the higher is the percentage of fat being utilized Although these assertions are generally correct, physiologists caution that if fat is being transformed to carbohydrate a low R Q is to be expected but the conditioning influences of the conversion process and the ultimate metabolism of the carbohydrate are not to be lost sight of

In uncontrolled diabetes the R Q tends to be low in keeping with the reduced amount of carbohydrate metabolized and with the acceleration of fat catabolism Insulin therapy reverses this trend and markedly so if an ample carbohydrate intake is maintained

The respiratory quotient can be determined for experimental purpose by measuring the amount of oxygen consumed and the amount of carbon dioxide produced per hour * Correction for the amount of protein metabolized is necessary before the nonprotein R Q can be calculated Each gram of nitrogen excreted in the urine assuming that the renal function is normal indicates that 6 25 gm of protein have been oxidized Knowing the total nitrogen excretion it is possible to calculate the oxygen and carbon dioxide that have to do with the metabolism of the protein and to deduct these amounts from the total respiratory exchange From this information and with a known R Q it is a simple matter to calculate the amounts of protein fat and carbohydrate oxidized over a given period The reader is referred to standard texts on physiology for further details

* According to Avogadro s law equal volumes of gases with the same pressure and temperature contain an equal number of molecules To metabolize 100 gm of glucose 75 litres of oxygen are required from outside i e for the oxidation of the carbon and 75 litres of carbon dioxide are produced The R Q is therefore $\frac{CO_2}{O_2} = \frac{75}{75} = 1$ In the combustion of fat rich in carbon and hydrogen and relatively poor in oxygen 200 litres of $O_2$ are needed and 142 litres of CO are produced The R Q is $\frac{142}{200} = 0\ 1$ (Best and Taylor)

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CHAPTER VIII

# Disturbed Physiology in Diabetes

**Introduction.** In diabetes the storage of glycogen in the liver and in the muscles is impoverished and the utilization of sugar by the tissues is reduced There are no detectable differences between the physiologic processes of the normal and those of the diabetic patient whose diabetes is under perfect control This fact presents the most logical reason for adequate control of the diabetes when it is possible to do so The disturbed physiology characteristic of diabetes occurs when the diabetes is "out of hand" and the degree of severity of the uncontrolled diabetes influences greatly the magnitude of these disturbances It is with this concept in mind that the abnormal processes are dealt with

The storage of monosaccharides, notably glucose, as glycogen, following their absorption from the small intestine and transit by way of the portal system to the liver, is greatly reduced in diabetes As a result large quantities of sugar gain access to the systemic circulation and this excess is made greater because of a reduced ability of the diabetic properly to utilize sugar The concentration of the blood sugar is increased to hyperglycemic levels and when these exceed the renal threshold—0 160 to 0 180 mg per 100 cc in venous blood—for variable periods glycosuria results Sugar is lost in the urine in amounts varying from minute traces to several pounds per day A unique type of starvation ensues—the extent of which is directly related to the amount of glycosuria

In moderately severe and severe diabetes sugar is lost in the urine even during fasting The sugar is derived from the diminishing supply of hepatic glycogen at first and later an emergency source, the body protein is tapped in nature's attempt to provide sugar for vital functions An index of the excessive protein breakdown is to be found in the increased excretion of nitrogen in the urine—each gram of urinary nitrogen indicates the metabolism of 6 25 gm of protein and the normal excretion of nitrogen in twenty four hours varies from 10 to 14 grams Quantitative determinations of the nitrogen excretion are not necessary in the clinical management of diabetes It suffices to know that in uncontrolled diabetes, of more than a mild degree of severity, body protein is being sacrificed, muscles become wasted and the patient's lassitude is intensified This loss of body protein

*has played a large part in making* poor risks of diabetic patients for surgical procedures in the past and in causing lowered resistance to infections, and in the development of other hormonal deficiencies occurring as a direct result of malnutrition

As the loss of sugar increases the metabolism of fat is also accelerated This is not detectable clinically in the early phase, as the peripheral tissues can metabolize a small increase of the ketone bodies which are transported to them after their production in the liver However, as the production of ketone bodies exceeds the amounts utilized in the peripheral tissues acetone bodies appear in the urine and finally in the blood in amounts detectable by crudely quantitative tests (see p 67) A digest of the clinical outcome of the disturbed physiology as it occurs in diabetes is presented in Table 8

TABLE 8

THE CLINICAL OUTCOME OF THE DISTURBED PHYSIOLOGY IN DIABETES

| | | | | | | |
|---|---|---|---|---|---|---|
| Hypoinsulinism (Diabetes) | → | Retarded ability to store and utilize glycogen<br>Overproduction of glucose by liver | → | Hyperglycemia and Glycosuria | → | Polyuria<br>Increased nitrogen excretion<br>Acetonuria<br>Hyperketonemia (Ketosis)<br>Dehydration<br>Demineralization<br>Loss of weight<br>Asthenia<br>Decreased resistance to infection<br>Degenerative disorders |

*The means are available to correct these deficiencies In the early phases* a normal status is promptly restored by insulin therapy and a suitable diet In the latter phase that of advanced ketosis, a reversion of the abnormal processes is still possible but at this stage the treatment is more complicated because of the dehydration and the disturbances in electrolyte balances which have intervened (see Chapter XVII)

The salient features of the chain of events which characterize diabetes mellitus as seen clinically are summarized as follows (*a*) *hyperglycemia* and *glycosuria* Among sequelae of these abnormalities are acetonuria, increased ketonemia (ketosis), polyuria dehydration demineralization, loss of weight asthenia and decreased resistance to infection (b) *Degenerative disorders* Diabetic retinitis and cataract, disease of the coronary arteries renal and peripheral vascular disease and the neuropathies are chronic complications of disturbed physiology over long periods The success in controlling hyperglycemia and glycosuria *will be rewarded by the* prevention or attenuation of these complications

**Hyperglycemia** The relative influences of a disturbed regulation of carbohydrate metabolism with *overproduction of glucose by the liver,* and with the failure to store glycogen to a normal degree, and *impaired utilization of glucose by the tissues* as causes of hyperglycemia are not entirely understood Soskin[1] champions the convincing overproduction theory in keeping with which insulin prevents overproduction of sugar by the liver

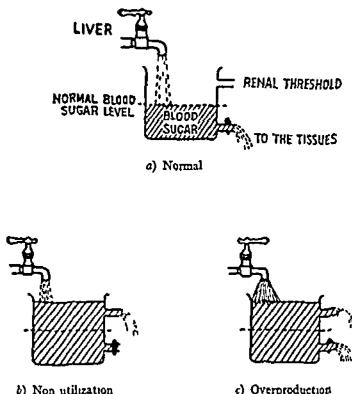



Fig 4 Diagrammatic analogy illustrating the non utilization and overproduction theories of diabetes (after Soskin) [1]

an inhibiting effect which is reduced in the insulin deficient state—diabetes *Hyperglycemia* ensues

The replacement of glycogen in skeletal muscles following physical exercise is retarded in uncontrolled diabetes " and as the skeletal muscles provide the overwhelming bulk of metabolically active tissues of the body this is of great significance All are agreed that insulin facilitates the transit of glucose into the tissues and facilitates its activity in cellular metabolism and that these activities occur as a direct result of increased phosphorylation made possible by insulin activity In uncontrolled diabetes these functions are profoundly disturbed and as a result the sugar is not withdrawn

from the blood as rapidly as under normal circumstances and with the liver releasing sugar at an increased rate *hyperglycemia* results

Nondiabetic hyperglycemia may occur following intracranial injuries (infection or trauma, in shock and following the administration of anesthetics) Hyperglycemia under these conditions is transitory, not lasting more than a few hours, and the mechanisms of its production are disturbed nervous control of releasing sugar from hepatic glycogen and stimulation of the adrenal medulla

**Glycosuria** Glycosuria, as detectable by the usual tests—Benedict's, Clinitest and Galatest—does not occur under normal conditions In the untreated diabetic glycosuria is the rule It is most frequent after meals and is least and may be absent before breakfast It usually occurs when the concentration of the sugar in the venous blood exceeds values of 160 to 180 mg per 100 cc Under unusual circumstances this so-called *renal*

TABLE 9

GLUCOSE CONTENT OF BODY FLUIDS NORMAL AND IN UNTREATED DIABETES

| FLUID | NORMAL | DIABETIC |
|---|---|---|
| | Glucose (mg per 100 cc) | |
| Whole blood | 60– 90 | 110–750 |
| Plasma | 70–110 | 130–800 |
| Serum | 70 110 | 130–800 |
| Lymph | 70–110 | 130–800 |
| Cerebrospinal fluid | 40– 70 | 75–400 |

*threshold* may be lower than 160 mg per 100 cc —a low renal threshold —and the glycosuria resulting in the nondiabetic under these circumstances is known as *renal glycosuria* or diabetes innocens—a poor term A low renal threshold occasionally is present as a complication of diabetes The relationships of blood sugar production, rate of utilization and hyperglycemia to the renal threshold are depicted schematically in Figure 4

Glycosuria is considered as being due to diabetes until proved otherwise, because it *is* due to diabetes much more frequently than to any other disorder and because, if the diagnosis of diabetes is missed, irreparable harm may be done The differential diagnosis of sugar in the urine *is dealt with on page 87*

The sugar contents of the various body fluids in normal and in diabetic subjects are indicated in Table 9

**Ketosis** Ketone bodies (aceto acetic acid, beta hydroxybutyric acid and acetone) are normally produced almost exclusively in the liver and transported in the blood for utilization by the tissues The quantities of ketones produced from fat far exceed those from other sources In fact the degree of ketosis is an index of the catabolism of fat and there being no reduc

tion in the ability of the peripheral tissues to dispose of ketone bodies in the diabetic an excess of ketone bodies in the blood must mean that they are being produced in abnormally large amounts

*Normal carbohydrate metabolism with* an adequate intake of carbo hydrate and total calories and normal stores of glycogen are the factors which prevent excessive breakdown of fat On the other hand, during star vation or in the case of uncontrolled diabetes, when large quantities of sugar are lost in the urine, less sugar is metabolized and glycogen storage is depleted As a result an increase in fat metabolism occurs

A liver with a good store of glycogen turns out sugar but when this store is depleted, and the fat content of the cells of the liver increases, the metabolic process becomes one of increased ketone production * When the accelerated production of ketone bodies exceeds the amount removed *from circulation by the peripheral tissues the excess, at first, is excreted* in the urine (*ketonuria*) Eventually when the excretory mechanism is un able to keep pace with the production the ketones accumulate in the blood (*hyperketonemia*), as occurs in diabetic coma Insulin is the most potent antiketogenic agent known It produces this effect by preventing the deposi tion of fat in the liver, by restoring glycogen storage in this organ and especially by facilitating the metabolism of carbohydrate, an effect which promptly reduces the excessive production of ketones

**Alloxan Diabetes** Islet cells of the rabbit's pancreas are selectively destroyed and diabetes is caused by a single intravenous injection of alloxan,[3, 4] 150 to 200 mg per kg of body weight Diabetes is produced in dogs when 50 to 75 mg of alloxan per kg are given Larger doses cause uremia plus diabetes An initial hyperglycemia lasting fifteen min utes to one hour follows the injection of the alloxan This, in turn is fol lowed by a marked hypoglycemia with convulsions The hypoglycemia is due presumably to insulin released from damaged islet cells Finally hyperglycemia and permanent diabetes ensue

*The damage to the islets is completed with great rapidity*—alloxan is not detectable in the blood for longer than five minutes after its injection intravenously

Alloxan diabetes is of great interest to investigators because Alloxan is chemically related to uric acid—a normal constituent of the body, the glutathione concentration normally present in the blood is greatly reduced *after the administration of alloxan*, glutathione administered in large doses protects against the *islet cell destruction by alloxan, transient diabetes* has been reported to follow the intraperitoneal injections of uric acid in rabbits,[5] but this only occurred when the blood glutathione levels were reduced by means of diets deficient in cystine and methionine and also

* Aceto-acetic (diacetic) acid is formed first It may be reduced to beta hydroxy butyric acid and this process may be reversed Acetone is an oxidation product of one or other of its precursors—diacetic acid or beta hydroxybutyric acid

on the basis that injections of purified adrenocorticotropic hormone (ACTH) produced in man a transient diabetes associated with a consistent co relation between loss of tolerance for carbohydrate, increased endogenous purine metabolism and depressed levels of blood glutathione[6]

The clinical significance of alloxan diabetes is that it permits the exploration of this problem from a new approach

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CHAPTER IX

# Pathology of Diabetes

## INTRODUCTION

Few diseases cause more widespread pathologic changes than does diabetes Most of the changes characteristically seen are those associated with premature aging the degenerative diseases of the arteries are outstanding Because of the inconstancy of cellular abnormalities the occurrence of normal tissues in patients with severe diabetes and the occurrence of the

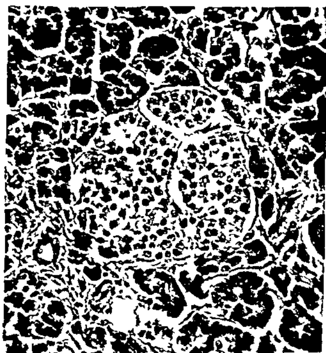


Fig 5. Normal islet of Langerhans.

occasional identical changes in the pancreas of the diabetic and of the non diabetic diabetes can be diagnosed on morphologic grounds alone in but a small percentage of cases

*The most consistent pathologic changes in diabetes are those of accel*

*erated degenerative processes* These are especially discernible in the circulatory system, the eyes, kidneys and nervous system Changes in the pancreas are disappointingly inconsistent

## PANCREAS

**A. Acute Changes** *Acute degenerative changes, notably hydropic degeneration* of the islets of the pancreas, can be produced in experimental diabetes A normal islet is illustrated in Figure 5, and acute hydropic degeneration of the islets—a reversible state—is depicted in

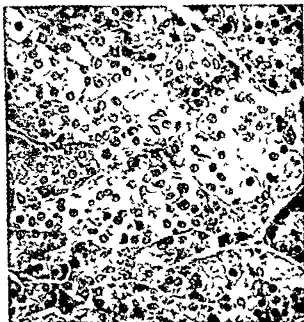


*Fig 6 An advanced stage of hydropic degeneration of the cells of the islets of Langerhans* (Courtesy of Dr F M Allen.)

Figure 6 Partial pancreatectomy—nine-tenths of the pancreas being removed—followed by overfeeding causes hydropic degeneration and, barring relief by appropriate treatment, exhaustion and death of the islet cells Also, in producing diabetes by injecting an extract of the anterior pituitary gland this form of degenerative change is noted[1] (p 5), and when hyperglycemia is maintained by the intraperitoneal injection of glucose, hydropic degeneration of the islets occurs (p 15) Hydropic degeneration does not occur in alloxan diabetes, in which case there is chemical destruction of the insulin producing cells—the *beta* cells—in contrast to the overworking exhaustion, and functional death of these cells brought about by overfeeding the partially depancreatized animal and by the ad

ministration of an extract of the anterior pituitary gland On the basis of these changes, observed at will in experimental diabetes, it is highly probable that hydropic degeneration of the islets occurs in nearly all, if not all diabetic patients at one time or another The fact that *hydropic degeneration* first noted by *Weichselbaum* (1901), is detected only occasionally *on examination of tissue secured at autopsy, or by biopsy, in the human* is no evidence that this degenerative change is not an essential feature in the development of clinical diabetes If one could select the time that would be most propitious for observing hydropic degeneration it would

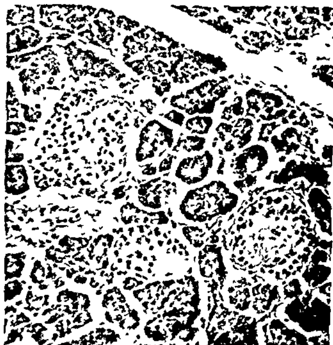


Fig 7 Bands of interacinar fibrosis and three islets which have undergone extensive hyaline degeneration (Courtesy of Dr F M Allen)

be in that period shortly after the onset of the clinical manifestations of diabetes and when the intensity of these manifestations were not modified by treatment, or during the progression of a fulminating diabetes The impracticability of this procedure doubtless deprives us of the positive proof that hydropic degeneration is an indispensable phase in the pancreatic change *in diabetic patients Hydropic degeneration* is an acute and transitory process

The destructive process of hydropic degeneration is, in some cases, accompanied by attempts at regeneration by the islet cells Mitotic figures may be seen, particularly at the periphery of the islet clusters That these

new cells may be more readily destroyed than the more mature cells by the functional overstrain that exists is possible and this phenomenon could explain why they do not save the situation Furthermore, the stimulus to new cell production may subside with control of the diabetes One might speculate that if it were possible to stimulate islet cell hyperplasia or re generation and yet keep the diabetes under control adequate cells might reach maturity in sufficient numbers to cure the diabetes There is much experimental evidence that, if there is adequate treatment before irrep arable degenerative changes have taken place hydropically degenerated cells can be redeemed and all manifestations of diabetes can be overcome

*Lymphocytic infiltration* of the islets occurs in children with severe diabetes and is considered as an acute process *Acute inflammatory changes* in the pancreas are not characteristic of diabetes and yet diabetes, on un common occasions follows repeated attacks of pancreatitis when most of the organ is destroyed

**B Chronic Changes** Chronic manifestations of diabetes are detected with greater frequency than are the acute and transient changes Among the chronic changes there is a *reduced number of islets of Langerhans* —although this is not invariably so—and in keeping with this, significantly less insulin is recovered from the pancreas of the diabetic—0 4 units per gram—than from that of the nondiabetic—1 7 units per gram

*Replacement of the islet cells by a hyaline substance* is the most com mon finding in autopsy material of diabetic patients (Fig 7) That this type of degeneration is not limited to the pancreas is well known The arteries and kidneys are particularly involved by the laying down of hy aline material Hyalinization of the islets is more common in patients over forty years of age but it is related more to the duration of the diabetes than it is to the age of the patient or to the degree of severity of the diab etes The source of the hyaline and the reason for its selective localization in the islets are unknown Hyalinization is a slow process but eventually it destroys the function of the islets which it invades and with progressive involvement of more and more islets the functional capacity of the insulin producing mechanism is reduced proportionately It is not known whether hyalinization is a cause of, or the result of diabetes

*Fibrosis* is next in frequency to hyalinization as a chronic change in the pancreas of the diabetic patient Also it is primarily a lesion of the islets and there is little extension into the acinar tissue It is present in slightly over half of these patients the cause of the fibrosis is not known extension is along the course of the vessels of the islets and it is most common in patients over forty years of age

**C Pancreatic Lesions with Secondary Diabetes** *Pancreatic cal culi* are uncommon They may be multiple and scattered throughout the pancreas or solitary with the calculus obstructing the duct of Wirsung

and, by setting up a retrograde autolysis, destroy the pancreas The acinar portion succumbs first and the islets later This is, surely, a rare cause of diabetes

Infiltration of the pancreas by *neoplastic growths* and by changes with deposits of iron as seen in *hemochromatosis* are uncommon causes of diabetes

## EXTRA PANCREATIC CHANGES

**Liver.** Fatty livers develop in diabetic animals maintained on a diet deficient in choline and without insulin [2] Fatty deposits also occur in the liver of untreated diabetic patients and more especially in the diabetic child These deposits disappear quickly and the size of the liver rapidly lessens when the diabetes is controlled adequately, especially when choline or one of its precursors is administered freely In the patient with uncontrolled *diabetes and impending coma, hepatic glycogen disappears from* the cytoplasm of the liver cells but the nuclei of these cells become engorged *with glycogen* These changes are reversible

**Skin.** The skin is an organ of considerable importance as a storehouse *for glycogen but in uncontrolled diabetes the glycogen stores in the skin* become depleted while the sugar content of the skin may be nearly treble that of the nondiabetic because of the systemic hyperglycemia Other cutaneous evidences that may be associated with diabetes and characterized by deposits of lipids—chiefly cholesterol—in the skin are xanthelasma palpebrarum xanthomas and necrobiosis lipoidica diabeticorum

Furuncles, carbuncles and pruritic disturbances are common complications of diabetes Infections of the skin were the most common complication in 514 consecutive diabetic patients admitted to the wards of the Pennsylvania Hospital (see p 212) because of acute complications Xanthochromia, a yellow discoloration of the skin of the palms of the hands soles of the feet and nasolabial folds, is due to a pigment derived from foods rich in carotene, notably the yellow foods e g, egg yolk, butter, carrots and sweet potatoes Diabetic patients who ingest more yellow foods than is normally the case are also more likely to exhibit xanthochromic deposits in the skin

[illegible] -s pre-
[illegible] atches
of waxy exudates, deposits of lipids, [illegible] rrhage and atheromatous changes in the larger and hyaline thickening of the media of the smaller arteries The source of the waxy exudates is not known but there are evidences that they are hyalinized deep retinal hemorrhages which result from venous stasis and rupture of veins Capillary aneurysms in the inner nuclear layer of the retina give the appearance of petechial hemorrhages [3] Superficial flame shaped hemorrhages are arterial in origin and occur more frequently in the hypertensive diabetic but hyper

tension is by no means necessary for this type of lesion to occur Increased capillary fragility is a common finding in these cases There is no apparent direct relationship between hypertension and the deep retinal hemorrhages of venous origin

A proliferative retinitis may take the form of a dense white fibrous membrane developing in hemorrhagic areas or the formation of new vessels to be seen most frequently about the optic disk Both of these abnormalities are distressingly common

The foregoing changes in the eyes are directly related to the duration of the diabetes and to the poor control which has been exercised over this



Fig 8 A normal renal glomerulus

disorder for long periods Cataracts, indistinguishable from senile cataracts are somewhat more common, but not strikingly so, in the older diabetics than in the nondiabetic population True diabetic cataracts are seen in young patients Fortunately they are rare

**Kidneys** *Intercapillary glomerular nephrosclerosis*, as described by Kimmelstiel and Wilson,[4] is of major importance because of its frequency and because the incidence of this complication is increasing In its advanced stage this disorder is indicative of diabetes There is a hyaline material laid down between the capillary loops progressing until all segments of the glomerular tuft are involved and forming rounded hyaline masses in the glomeruli Multiple segments of the tufts may be involved

with eventual replacement of the entire glomerulus (Fig 9) A normal glomerulus is illustrated in Figure 8 An advanced degree of arterio sclerosis with its subintimal deposits of hyaline substance is usual in these cases (*Figs 10 and 11*) The clinical counterpart is indicated by edema arterial hypertension and albuminuria The reduction of renal function ultimately causes uremia This disease process occurs in a mild form in both diabetic and nondiabetic subjects It may remain relatively stationary for long periods but when the edema and albuminuria are of great degree and the serum albumin is reduced the duration of life is measured in months and not in years



Fig 9 *Intercapillary glomerulosclerosis in diabetes mellitus Note characteristic* nodular hyaline thickening in one segment of the tuft and the diffuse intercapillary sclerosis

*Arteriosclerosis* involving the renal arterioles is the most common renal disorder associated with diabetes In diabetic patients over fifty years old it is found in 77 6 per cent or about five times as frequently as in non *diabetic controls*[5] *The characteristic changes, i e* subintimal deposits of hyaline are much more intense in diabetic subjects In fact thick homogenous deposits of hyaline substance in afferent and efferent renal arterioles present strong presumptive evidence of diabetes This change illustrated in Figures 10 and 11 is contrasted with normal renal arterioles as depicted in Figure 12

The degree of arteriosclerosis appears to have a direct relation to the degree of arterial hypertension in patients under fifty years of age though arteriosclerosis occurs even in severe degrees (Fig 11) in diabetic pa

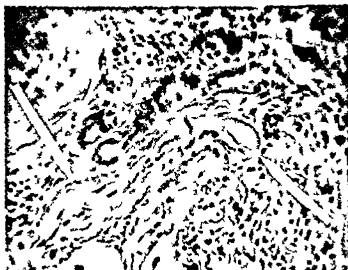


Fig 10 Arteriosclerosis of an afferent arteriole leading into a glomerulus (lower right) in a kidney of a diabetic patient

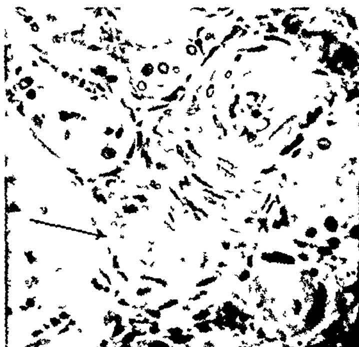


Fig 11 Severe renal arteriolar sclerosis in a diabetic patient

tients without hypertension In individuals over fifty years of age the degree of involvement is related more to advancing age than it is to the degree of hypertension

There is good evidence that diabetes in some manner, intensifies the speed and degree with which the hyaline deposits in the arterioles are made

*Malignant hypertension* a rapidly progressive form of hypertension with uremia secondary to thrombonecrosis glomerulitis or intimal fibro

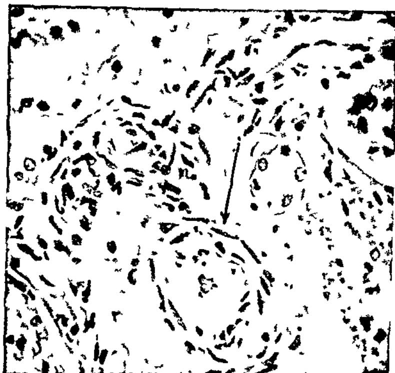


Fig 12 Normal renal arterioles.

sis, may be encountered in association with diabetes but there is no specific relationship between the two diseases

*Pyelonephritis* is a common complication of diabetes Of 60 of our diabetic patients coming to autopsy between 1927 and 1942 21 had evidences of active or healed pyelonephritis The disease may take an acutely destructive form—necrotizing renal papillitis—with extensive abscess formation and necrosis of the papillae[6]

*Arteriosclerotic changes in renal arteries* occur in diabetics with greater frequency than in nondiabetic subjects but morphologically the disorder is the same in both

**Arteries** Lesions of the vascular system are responsible for the deaths

in more than 50 per cent of patients who have diabetes for more than fifteen years Sclerotic changes in the coronary arteries predominate as do similar changes in the arteries of the pelvis legs and feet (Fig 13) Irreversible changes are represented by swelling and hyaline degeneration of the ground substance of the intima and the infiltration of lipids and subsequent calcification These processes—atheromatous and arteriosclerotic—are seen most frequently in the aorta the coronary arteries and the vessels of the extremities Hence the predisposition to occlusion of the coronary arteries and to occlusive vascular disease of the extremities is not surprising

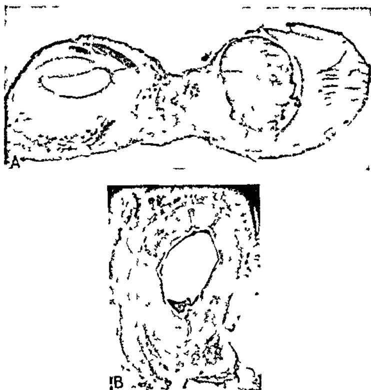



Fig 13 A A section of two medium sized arteries near their junction. Each shows a marked encroachment of the lumen by a hyaline thickening of the intima and one shows in addition the occlusion of the lumen by a thrombus

B A section of a normal artery of approximately the same size is shown for comparison.

A third type of vascular degeneration involves the medium sized vessels causing irregular medial necrosis and calcification without lipid deposition This is Monckeberg's sclerosis

**Nervous System** Not much is known of the pathologic changes in the neurologic complications of diabetes Demyelinization of the nerves occurs in cases of *diabetic neuritis* which is the predominating acute and reversible neurologic complication of diabetes The degenerative changes of the *diabetic neuropathies*—the characteristically chronic neurologic complications—occur in the peripheral nerves anywhere in the entire nervous system, and in the spinal cord particularly in the posterior and lateral columns and are identical with those seen in pernicious anemia These changes account for the disturbances in sensation the so-called diabetic tabes and in rare cases, changes in the bones and joints of the feet indistinguishable from Charcot s joints and trophic ulcers of the feet (see p 207) These neurologic changes have been attributed to arteriosclerosis This is not the whole answer however as they occur in some instances in the absence of significant arteriosclerosis Infection is the apparent cause in some but not all cases The degenerative changes of advanced degree in which the process may be irreversible are distinct from those in which acute inflammatory changes predominate The acute changes as seen in neuritis are readily cured primarily by control of the diabetes and less frequently by correction of dietary deficiencies notably a deficiency of vitamin $B_1$.

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CHAPTER X

# The Urine and Blood in Diabetes

## THE URINE

**Glycosuria** In general, the term "glycosuria" is loosely used to mean sugar in the urine in the broad sense and is not restricted to glucose in the urine as occurs in diabetes A relatively innocent glycosuria occurs in some nondiabetic subjects who have permanently low renal thresholds for glucose, and others whose renal thresholds are temporarily reduced as occurs during pregnancy and in hyperthyroidism Other sugars, as discussed on page 90, may be excreted in the urine but this is an uncommon occurrence and is of little or no clinical significance

Glucose, a fermentable, dextrorotatory, copper reducing sugar appearing in the urine in amounts demonstrable by the Benedict and other tests* in common use, should be considered as being due to diabetes until proved otherwise It is a simpler matter to establish the diagnosis of diabetes and thereby identify the sugar as glucose indirectly than it is to identify the sugar by chemical means A search for hyperglycemia after the strain of a meal usually will give the answer if the patient has diabetes but if doubt still exists the special tests presented in Chapter XI are resorted to Glycosuria is the most common, though not the most sensitive indication which leads ultimately to the diagnosis of diabetes mellitus Ordinarily glycosuria is the result of hyperglycemia, sugar being lost when the venous blood sugar level exceeds the renal threshold, usually between 160 and 180 mg per 100 cc Glycosuria is of special importance because it is tested for in the conduct of a routine urinalysis, hence the chance of its discovery is great and the detection of the diabetes is more likely in contrast with the more delicate, but less frequently performed, test for diabetes viz., determination of the level of the blood sugar

There is a copper reducing substance in normal urine but the quantity is so minute that it escapes detection by the usual tests Sugar occurring in the urine in concentrations below 0 1 per cent may be considered as normal Glucose when boiled with an alkaline copper solution (Benedict's test, p 67) reduces the copper to cuprous oxide, thus changing the color of the solution from blue to green greenish yellow, orange or brick red

* Clinitest and Galatest, see p 67

with increasing concentrations of sugar Ordinarily, glucose occurring in sufficient quantities in the urine to be detected *by the Benedict test indicates* a pathologic condition Glycosuria may occur in some normal persons for short periods after an unusually great carbohydrate intake This is *alimentary glycosuria* and may be attributed to a lowered renal threshold or to absorption of glucose from the intestine at a rate too rapid for its prompt removal from the circulation Starving individuals may have glycosuria upon the resumption of feeding (*hunger glycosuria*). These are innocent forms of glycosuria

The glycosuria which occurs as the result of diabetes varies from scarcely detectable traces to large amounts, 10 per cent or more It is unusual, however, to find a concentration of sugar in the urine of diabetic patients in excess of 10 per cent For practical purposes *qualitative tests* (p 67), which are crudely quantitative also, applied to fractional collections of urine serve admirably as guides in adjusting the insulin dosage More will be said of this in the section on treatment

*In the case of a patient having a mild diabetes, glycosuria is most likely* to occur during the daytime and in the evening, that is, during the time of day when three meals are taken in fairly close succession Under these circumstances glycosuria is least likely to occur in the morning before breakfast—at the end of the longest period without food—and *an evening specimen, not the first one voided in the morning, is the one most likely to contain sugar* In contrast, the severe grades of diabetes cause continuous glycosuria until corrected by appropriate treatment

When sugar is found in the urine, and the blood sugar values are normal, both before (fasting) and two hours after a liberal meal, and when the patient is subjected to a glucose tolerance test, the diagnosis of a non diabetic *melituria is justified*

*False positive reactions* to tests for glycosuria are common The copper used in qualitative tests for glycosuria is slightly reduced and may be mistaken for sugar when large quantities of conjugated glycuronates occur in the urine They appear in decomposing urine and may be avoided by examining freshly voided specimens The glycuronates appear in the urine in considerable quantities and give a mildly positive Benedict's test after the ingestion of salicylates, menthol, chloral hydrate, morphine and amino pyrine As a group, the glycuronates reduce the copper in Benedict's and Fehling's solutions but, unlike glucose, are nonfermentable

The homogentisic acid of alkaptonuria reduces the alkaline copper solutions, thus giving false positive tests for sugar In this disorder, if the urine is allowed to stand and become alkaline by ammoniacal putrefaction or if alkali is added, it assumes a black or gray color Alkaptonuria is a rare condition

*Tests for Glycosuria For mass examinations, for office and clinic prac*

tice, the following simplified tests for sugar and acetone in the urine are satisfactory Also they are employed as routine by diabetic patients who test their own specimens

CLINITEST FOR GLYCOSURIA * This convenient modification of Trommer's test permits a qualitative, and crudely quantitative, test, for sugar in the urine The test is made by placing 5 drops of urine in a test tube, the dropper is rinsed and 10 drops of water are added, then *one* Clinitest reagent tablet—containing anhydrous copper sulfate, anhydrous sodium hydroxide citric acid and sodium bicarbonate—is added Heat is generated by the chemical reaction in the tube causing the solution to boil The test tube is not to be shaken while the solution is boiling The result is read after the boiling has ceased for at least fifteen seconds There is no sugar in the sample tested if the resulting color is blue Sugar is present if the final color is dark green, yellow, orange, brown or rust red The amount of sugar present, up to 2 per cent, can be determined with a fair degree of accuracy by contrasting the color obtained with the standard color scale

CALATEST FOR GLYCOSURIA † This test for sugar in the urine is accurate, simple, requires no boiling and gives a prompt reaction It is performed by placing on a piece of plain white paper an amount of the Galatest reagent—containing a bismuth salt, sodium hydroxide and sodium silicate—sufficient to cover one third of a dime To this is added one small drop of urine The result is read after thirty seconds have elapsed If the powder takes on the amber color of urine the specimen tested contains no sugar The color changes from a light gray to black with increasing concentrations of sugar The approximate amount of sugar present is estimated by comparing the color obtained with the standardized color scale

BENEDICT'S QUALITATIVE TEST FOR SUGAR IN THE URINE (MODIFIED)

*Equipment*

1 Qualitative Benedict's Solution (when purchasing testing solution, specify *Qualitative* Benedict's Solution as Benedict's Quantitative Solution does not change color when boiled with glucose)

2 Test tubes marked at 5 cc and 2 5 cc levels

3 Dropper pipette

4 Water bath

*Technic*

1 Put 2 5 cc (approximately ½ teaspoonful) of Benedict's Solution in a test tube

2 Add 4 drops of the urine to be tested Hold pipette perpendicularly while adding drops

* Materials for this test may be secured from Ames Company Inc Elkhart Ind

† Calatest equipment is obtainable from the Denver Chemical Mfg Co Inc., 163 Varick St New York 13 N Y

3 *Shake tube to mix urine and Benedict's Solution thoroughly*
4 Put the tube in a water bath of boiling water and boil for five minutes
5 Let cool and read reaction

*Interpretation*

Clear blue solution No sugar
Light greenish yellow Faint trace of sugar
Yellow to orange Moderate amount of sugar, about 1 per cent
Chocolate brown to brick red Large quantities of sugar, over 2 per cent

This test has the advantage of being inexpensive

*Millard Smith's Micro Modification of Benedict's Quantitative Test for Sugar in the Urine*

In clinical practice the exact quantitative determinations of sugar in the urine are not often necessary but this simplified method of obtaining this information if desired is included for the sake of completeness

*Equipment*

1 One small ring stand with test tube clamp a micro Bunsen burner or small alcohol lamp
2 A Pyrex test tube (18 by 160 mm)
3 A Millard Smith pipette No 2 and a 1 cc Ostwald pipette

*Technic*

1 Transfer 1 cc of Benedict's *quantitative* solution to the test tube (held in ring clamp) and add 0 2 to 0 7 gm of anhydrous sodium carbonate Bumping is prevented by adding a thoroughly dried pebble a piece of quartz or a pinch of talcum powder
2 The mixture is raised to and kept at the boiling point
3 The urine is added slowly from the Smith pipette until all of the blue color disappears Care should be taken to allow time for complete reduction before adding more urine The test is done slowly and care must be taken not to pass the end point The percentage of sugar present is read directly from the pipette without calculation Urine containing less than 1 per cent of sugar is titrated directly When larger amounts of sugar are present the urine is diluted 1 10 or 1 20 before titration

**Specific Gravity.** The specific gravity of the urine usually increases in direct proportion to the amount of sugar present A specific gravity of 1 030 or above, obtained on a pale urine is almost without fail, due to sugar The specific gravity is restored to normal when the glycosuria is corrected However, a normal specific gravity, 1 010 to 1 025, is common even though glycosuria is present

**Urine Volume.** In untreated and symptomatic diabetes the twenty four hour urine volume characteristically exceeds the average normal of 1500 cc In fact, the quantities may reach several gallons The great increase in the volume of urine gives but little index of the severity of the diabetes but, in general, the greater the volume the greater is the amount of sugar present Occasionally the polyuria is so great that amounts totaling more than 50 per cent of the body weight may be voided in twenty four hours Control of the diabetes restores the rate of urine excretion to normal

**Ketonuria.** Ketonuria is the first recognizable sign of ketosis though it is of little importance in the diagnosis of diabetes It results when, from

a lack of insulin, the metabolism of carbohydrate is reduced, the metabolism of fat is accentuated and ketones are produced in greater than normal quantities *Ketones are also derived from certain amino acids* Ketonuria occurs in a mild form in healthy nondiabetic subjects whose food intake, especially the carbohydrate, is greatly curtailed Ketonuria, caused by diabetes, is common without other evidence of ketosis This was an especially common finding in the pre-insulin era when diets high in fat and low in carbohydrate content were the rule A considerable quantity of ketones may be excreted in the urine without their accumulation in the blood or without a reduction of the carbon dioxide combining power Failing appropriate treatment, however, the rate of the production of ketone eventually exceeds the rate at which they can be excreted It is then that qualitative reactions for acetone and diacetic acid in the plasma, or serum become positive and it is then that the acetone odor appears on the breath An extremely rare exception to this rule is seen when, with renal disease small amounts only of acetone appear in the urine when large quantities are retained in the blood

The ketone bodies are *acetone*, *diacetic acid* and *beta hydroxybutyric acid* Acetone and diacetic acid appear under similar conditions Both are identified by a modified Rothera test,* or more convenient still the "Acetest"†

An increasing loss of beta hydroxybutyric acid in the urine accompanies a deepening ketosis In severe ketosis it is in this form that most of the ketones are lost amounting to as much as 200 gm in twenty four hours The tests for acetone and diacetic acid in the urine are strongly positive before appreciable amounts of hydroxybutyric acid are excreted

Ketonuria is a guide for further investigation The amount of ketones excreted is of less immediate importance than the amount of these products which has accumulated in the tissues and in the blood It has been shown that mild degrees of ketonuria may persist for months and years without apparent harm whereas, a 4 plus reaction for ketones in the blood from a patient who also has glycosuria is ample evidence to make a diagnosis of diabetic coma

*Qualitative Tests for Acetone* (a) THE "ACETEST" TEST This test for acetone is a simple and reliable test which merely involves the adding of a drop of freshly voided urine or freshly secured sample of plasma or

* Bedside test for plasma acetone and diacetic acid (Rothera Wishart) Two drops of plasma or serum are placed in a Wassermann tube and supersaturated with ammonium sulfate crystals and shaken Two drops of approximately 5 per cent sodium nitroprusside solution are added and shaken Two drops of ammonia water are added and shaken Allow to stand for three minutes

| | | | |
|---|---|---|---|
| Interpretation | Permanganate color | — | trace of plasma acetone |
| | Light blue | — | moderate |
| | Deep blue or almost black | — | heavy reaction for plasma acetone |

† Acetest reagent tablets are manufactured by Ames Co Inc Elkhart Ind

serum to a tablet which contains amino acetic acid, disodium phosphate and sodium nitroprusside The color of the tablet is noted after thirty seconds have elapsed Interpretation of the test

| | |
|---|---|
| White or cream color | negative test |
| Purple tint | 1 plus reaction |
| Lavender | 2 plus reaction |
| Moderate purple | 3 plus reaction |
| Deep purple | 4 plus reaction |

(b) ROTHERA'S TEST * To 5 or 10 cc of urine add about 1 gram of ammonium sulfate and 2 or 3 drops of fresh concentrated sodium nitroprusside solution and overlay with strong ammonia A reddish purple ring shows the presence of acetone

(c) ACETONE TEST (DENCO) This simple and accurate test for acetone is executed by *depositing on a dry white paper sufficient of the Acetone Test* (Denco) reagent—containing sodium bicarbonate, ammonium sulfate and sodium nitroprusside in anhydrous form—to cover one third of a dime and by moistening this *entire amount* of powder with 2 or 3 drops of urine to be tested In the presence of acetone a shade of purple will develop within thirty seconds, a trace of acetone yields a light lavender color and with increasing amounts the color will be darker, a dark blue indicating a 4 plus reaction *In the absence* of acetone a grayish yellow color is the result

We use this test routinely in examining the urine and the blood plasma or serum, for acetone

(d) QUALITATIVE TEST FOR DIACETIC ACID IN THE URINE (GERHARD'S TEST) To a few cubic centimeters of the urine add 10 per cent aqueous solution of ferric chloride, drop by drop, until the phosphates are precipitated, filter and add more of the ferric chloride If diacetic acid is present, the urine assumes a Bordeaux red color Clinically, we do not employ the test for diacetic acid but rely on the tests for acetone as indication of the *degree of ketonuria*

## THE BLOOD

**Sugar Content.** *Hyperglycemia is the most decisive indication of diabetes* Without it the diagnosis cannot be made with certainty A concentration of sugar in a specimen of venous blood, taken after an eight to fourteen hour fast, in excess of 130 mg per 100 cc, or a value exceeding 170 mg after a hearty meal is usually due to diabetes There is practically no difference in the sugar concentration in venous and arterial (capillary) blood in the postabsorptive (fasting) state After a meal, how

* Todd and Sanford Clinical Diagnosis by Laboratory Methods, 11th Ed, W B Saunders Company, Philadelphia 1948

ever, and in the normal person the arterial blood sugar level is from 20 to 50 mg per 100 cc higher than that in the venous blood This difference represents utilization of sugar by the tissues and the difference is reduced in untreated diabetes and the normal variation is restored by adequate treatment

A diagnosis of diabetes should never be made on the basis of a single blood analysis unless the hyperglycemia is accompanied by glycosuria and characteristic symptoms The most certain criteria of diagnosis are repeatedly elevated fasting blood sugar values and glycosuria It is significant that in the patient with an untreated but mild diabetes glycosuria tends to subside toward morning—at the end of the longest period without food It is then also that the blood sugar level is the lowest in the twenty four hours

Sugar is present in the blood of normal persons in concentrations varying from 70 to 110 mg per 100 cc fasting (according to the Folin Wu method) There are slight differences in the values according to the method of determination employed but clinically these differences are insignificant The blood sugar levels in the average untreated diabetic patient without acute complications range between 180 and 300 mg per 100 cc (Folin Wu method)

The hyperglycemia and glycosuria of diabetes behave in a characteristic manner Liberal additions to the carbohydrate and total caloric intake tend to increase their severity, while restricted carbohydrate and total food allowance have the opposite effect

Hyperglycemia may be present for only short periods, two to four hours after each meal with normal fasting values in patients having mild diabetes The likelihood of identifying these mild cases is enhanced by taking the blood specimen for determination of the sugar value two hours after the biggest meal of the day Values in excess of 170 mg per 100 cc and an accompanying glycosuria make the diagnosis obvious

The degree of hyperglycemia alone is not an accurate index of the severity of the diabetes An untreated obese patient may have a blood sugar level of 500 mg or more per 100 cc and yet the mildness of the diabetes is apparent when the hyperglycemia is promptly corrected by merely restricting the total food intake It is a reliable rule to consider that *every untreated overweight diabetic patient has a mild diabetes despite the degree of the hyperglycemia that is found* In contrast the underweight patient with untreated diabetes has a severe diabetes though the blood sugar level may not exceed 250 mg per 100 cc To restore the underweight patient to good health a gain in weight is imperative This end is achieved only by a liberal food intake and insulin therapy *To repeat the level of the blood sugar is not a reliable index of the severity of the diabetes* The degree of hyperglycemia in the light of the relationship of the patient's weight with that of the normal is a more reliable guide *The fat diabetic patient has a*

*mild diabetes and the lean diabetic patient with a persistent fasting hyperglycemia has a severe diabetes* It is well, in most instances, to delay giving an opinion on the severity of the diabetes in underweight patients until repeated blood sugar values are known and their response to appropriate treatment is observed

Other departures from the normal composition of the blood (Table 10) are not of special value in arriving at a diagnosis of diabetes They are *for the most part, observed during complications of this disorder and will* be dealt with under the respective complications We refer to alterations in the hemoglobin, the urea nitrogen, concentration in the blood plasma acetone, carbon dioxide combining *power, plasma or serum chlorides, the* blood volume as seen in ketosis, and cholesterol and fatty acid values

TABLE 10]

ALTERATIONS IN THE COMPOSITION OF BLOOD ASSOCIATED WITH DIABETES MELLITUS†

| CONSTITUENT | NORMAL RANGE | IN UNTREATED DIABETES |
|---|---|---|
| [illegible] | [illegible] | [illegible]n ketosis |
| [illegible] | [illegible] | [illegible]n ketosis |
| [illegible] | [illegible] | [illegible]n ketosis |
| [illegible] | [illegible] | [illegible] ketosis |
| [illegible] | [illegible] | [illegible] ketosis |
| Urea nitrogen (mg /100 ml ) | 9 6– 17 3* | Increased in ketosis |
| Potassium—as K (mEq /L) | 3 8 4 3* | Increased in untreated ketosis |
| —as mg /100 ml | 14 8 16 8 | Decreased after onset of treatment for ketosis |
| Sodium—as Na (mEq /L) | 133 6–136 3 | Decreased in ketosis |
| —as Na (mg /100 ml ) | 307 5–316 | Decreased in ketosis |
| Sugar—as total reducing substance arterial whole blood ** (mg /100 ml ) | 80 –110* | Increased |
| venous (mg /100 ml ) | 70 100* | Increased |
| Cholesterol—Total (mg /100 ml ) | 150 –190* | Increased |
| Fatty acids—Total (mg /100 ml ) | 290 –420 | Increased |
| Lipid Phosphorus—Lecithin (mg /100 ml ) | 12 – 14 | Increased |
| Total acetone bodies (as acetone) (mg /100 ml ) | 1 3 2 6 | Increased in ketosis |
| Acetone—qualitative test on plasma | negative | ++++ in diabetic coma |

* Extracted from Sunderman and Boerner s Normal Values in Clinical Medicine W B Saunders Company, Philadelphia 1950

** Blood is taken from the finger tip or from the lobe of the ear

† The values are those obtained on plasma or serum taken under fasting conditions unless otherwise indicated

NOTE In the clinical management of diabetes the common studies are those of blood sugar cholesterol $CO_2$ and plasma acetone

CHAPTER XI

# Symptomatology, Physical Signs and Diagnosis of Diabetes

## A. SYMPTOMATOLOGY

The symptoms of diabetes may be classified into three groups (a) those of uncomplicated diabetes, and diabetes with (b) acute complications and (c) chronic complications

(a) **Uncomplicated Diabetes.** The symptoms associated with uncomplicated diabetes are fatigue, polyuria, polydipsia, polyphagia, loss of weight and pruritus The onset of symptoms, in presumably uncomplicated diabetes, is usually insidious but it may be abrupt—so abrupt indeed that the date of onset can be clearly recollected This latter manner of onset is most frequently encountered in the young diabetic patient

(b) **Acute Complications.** Rapid intensification of the symptoms of uncomplicated diabetes plus an *acute infection* e g, carbuncle, furuncle, infection of the respiratory tract and the symptoms that characteristically develop as a result of the respective infections Failing corrective measures, anorexia, nausea and vomiting, dryness of the mouth, drowsiness, abdominal pain and coma, all being symptoms of *diabetic ketosis,* may develop gradually over several days with no other apparent complication, but usually they develop rapidly—in a matter of hours—and an acute precipitating complication is usually detectable An *occlusion of a coronary artery* with the characteristic substernal pain is among the common acute complications of diabetes

(c) **Chronic Complications.** The symptoms associated with, and due to, chronic complications are, for the most part, indicative of degenerative changes and these are largely of the vascular system

Dimness of vision, sudden or gradual, of mild or severe grade, and, less frequently, headaches are symptoms which suggest *diabetic retinitis, cataracts* and *glaucoma*

Substernal pain or numbness, or pain in the left shoulder and arm precipitated by exercise, and promptly relieved by nitroglycerin therapy, indicate *insufficiency of the coronary circulation*

Weakness, nocturia, swelling of the ankles with hypertension albuminuria and retinitis are signs of *intercapillary glomerulosclerosis*

Pain along the course of a *nerve, burning, numbness, tingling* aches and bizarre widespread pains, particularly in the legs and feet and occurring at night, paralysis, tabetic manifestations with disturbed sensation in the feet, disturbed efficiency in sweating and impotence occur in *diabetic neuropathy*

*Irregular menses or amenorrhea, relative* sterility, and various difficulties attending pregnancy in the diabetic attend the *hormonal disturbances* of diabetes

Pain in the calf muscles on exertion which is relieved by rest (intermittent claudication), coldness and cramps in the extremities, paresthesias with development of cyanosis in the feet when placed in the dependent position and with pronounced pallor when elevated, with or without evidences of gangrene, signify *advanced peripheral vascular disease*

The complications of diabetes and their varied symptomatology are dealt with in Chapter XV The more important complications and the symptoms to which they give rise are presented here for the sake of completeness but also because the only presenting symptom that may lead to the detection of the diabetes is often a symptom of some complication

## *Special Consideration of Symptoms*

Symptoms may suggest a diagnosis of diabetes but nothing more On the other hand, the finding of glycosuria, an initial step toward a diagnosis is not infrequent in the absence of classical symptoms

The varied symptomatology of diabetes in a typical case is at once indicative of some systemic disorder General weakness, loss of weight, excessive appetite and thirst, the frequent passing of large quantities of urine without discomfort, rising at night to void, pruritus (which in the female occurs particularly about the vulva), and backache are the most common symptoms of uncontrolled and uncomplicated diabetes Loss of libido with impotence in the male is less common than the foregoing classic symptoms but is more frequent than is generally supposed Direct questioning of patients may be required before this complaint is elicited

It has been estimated that as high as 12 per cent of patients having diabetes have no symptoms of this disorder This observation is based on the finding of glycosuria in applicants for insurance and those undergoing routine health examinations There is no doubt that many persons who *are free from symptoms* have a mild diabetes of which they are ignorant We are incredulous, however, of the value of figures based on applicants for life insurance who state that they have no symptoms

**General Weakness** This may be the only symptom of diabetes It has been the most common presenting complaint of our diabetic patients This symptom, common to so many debilitating diseases gives little indication of the nature of the underlying disorder It is a symptom, however, that

deserves serious consideration and it is a good practice to investigate thoroughly each patient who complains of it

**Loss of Body Weight** A rapid loss of body weight in the afebrile patient, especially in the young diabetic patient, is common This symptom is readily accounted for Glycosuria occurring in amounts varying from mere traces to as much as 15 per cent accounts for a good portion of the loss of weight Glycosuria causes a peculiar form of starvation but accounts for the seeming paradox which exists when, with increased appetite for food, the intake greatly exceeds that of the normal and yet a loss of weight continues There is an *excessive breakdown of protein* as indicated by the abnormally large quantities of nitrogen excreted in the urine Loss of weight is due, in part also, to the loss of body water by the *diuresis* resulting from the effect which the high concentration of sugar in the blood exerts on the renal tubular epithelium Further loss in weight is encountered in the presence of *ketosis* in which an increased degree of dehydration, and loss of nourishment, in the form of ketones, are additional factors This feature is dealt with in the section on complications

Great importance attaches to body weight and its changes in diabetes A person with untreated and uncontrolled diabetes may lose weight while partaking of an unrestricted diet *During this process the diabetes tends to become more severe, hence, loss of weight in this manner is injurious* This is true even in the case of the obese patient because it leaves less weight to be reduced by a method which improves and controls the diabetes This latter and beneficial method of reducing weight is brought about by curtailing the patient's total food intake—exactly as one would reduce an obese nondiabetic patient This restriction lessens the immediate demand on the islet function of the pancreas and at the same time consolidates this gain, since it reduces the total metabolism by virtue of the reduced body weight which ensues Risking monotony in repetition concerning one of the most important aspects of clinical diabetes we re state *A loss of weight, i e a decrease in total metabolism secured by the restriction of the total diet, decreases the food loss gives the pancreas functional rest, affords the overweight patient with uncontrolled diabetes a remarkable improvement in carbohydrate and total food tolerance and brings the diabetes under control without the administration of insulin*

*A loss of weight due to the activity of the diabetes, whether due to ignorance or wilful neglect, destroys food tolerance, the diabetes becomes more severe, and the need for insulin increases* An obese patient who becomes underweight because of the activity of the diabetes loses all of the advantages that go with a reduction in weight by appropriate treatment, and the necessity of using insulin indefinitely is usually inescapable We hope this is clear It is of vital importance It represents one of the fundamental considerations of diabetes, the understanding of which we owe to Dr Frederick M Allen

**Excessive Appetite and Thirst.** These symptoms occur in direct relation to the amount of glycosuria and the polyuria until ketosis intervenes As ketosis develops anorexia replaces the polyphagia Excessive appetite is a compensatory effort to replace lost nourishment, polydipsia, to replace lost fluids The thirst and the frequent voiding of large amounts of urine are among the most common symptoms of diabetes occurring in about three quarters of all cases It is in this group of patients that back ache is common This symptom can be reproduced in a normal person by having him drink large quantities of water Distention of the renal capsule by increased activity of the kidneys with greater than usual volumes of fluid passing through them apparently is responsible

The physician who recognizes diabetes early does his patient a great service No reliance is to be placed on the absence of symptoms One has but to consider how much so many patients owe to chance examinations for other disorders, routine or insurance examinations, to realize this Diabetic patients who are free from symptoms are not immune to complications, nor is the diabetes innocent in such cases

Complications of diabetes often prompt the patient to seek treatment The discovery of diabetes, of the presence of which the patient may be entirely ignorant, is often made on such consultations

## B PHYSICAL FINDINGS IN DIABETES

Many diabetic patients are *obese* but many have no physical evidence of the diabetes from which they suffer However, the more carefully the examination is made, the more often will the search be rewarded by the discovery of abnormalities which, when correlated with the symptoms, are found to be more or less characteristic We refer especially to the *fatigued appearance,* the *looseness* and *wrinkling of the skin* observed in patients who have *lost weight,* and to *dryness* of the skin in those patients who suffer from excessive thirst and polyuria There is a mild degree of *pallor* of the skin of the face in many diabetic patients This is particularly noticeable in those who are overweight, are past middle age, and who have advanced disease of the arteries This may be attributable to the elevation of the blood lipid concentrations, but in most instances it is probably due to vascular disease It is especially common in patients suffering from disease of the coronary arteries In the young patients, particularly females, taking large amounts of insulin, the skin may have a waxy *transparency* with a smoothing out of wrinkles of the face This has been referred to as an ' insulin face ' It is noticeable shortly after insulin therapy is begun and is due to water retention in the skin This condition tends to disappear when the diabetes is controlled over a period of months We can recall, however, several young women in which this state remained unchanged for several years

Other skin disorders may occur as a result of the diabetes namely, *xanthelasma palpebrarum* and, rarely, *xanthoma diabeticorum* and *necrobiosis lipoidica diabeticorum*

Though all shades of health from the robust, normal appearing diabetic patient to one critically ill with ketosis are observed, it is well to emphasize that most physical abnormalities observed in these patients are due to complications of diabetes The untreated diabetic patient is especially susceptible to *gingivitis, pyorrhea alveolaris* and to *staphylococcic infections* e g , furuncles, carbuncles and bacteremia He is more prone than the non ... *tuberculosis* This complication is most ... coma ... diabetic coma showed evidences of ... Boucot, Cooper and Richardson[2] found tuberculosis to be twice as common in 3106 diabetic patients surveyed as in a similar nondiabetic group

The *degenerative changes* are readily detected on physical examination especially *cataracts diabetic retinitis* and *generalized disease of the arteries Coldness of the extremities cyanosis of the feet in the* dependent position *and a cadaveric* pallor *when they are* elevated, *gangrene of the toes*, heel or other parts of the feet occur as a result of extensive changes in the arteries *Irritation of the* skin may be generalized but occurs most frequently about the genitalia as a result of pruritus, which is common, as are *epidermophyton* infections The *fungus* infections involve the feet, between the toes most *frequently* but may be found elsewhere on the body

The physical signs of *diabetic coma* are considered in detail elsewhere but because signs of this complication should be looked for in every acutely ill diabetic patient they are summarized here as follows marked dehydration an odor of acetone on the breath, "air hunger" (Kussmaul's respiration) reduced *intra* ocular tension, dry skin and mucous membranes, low blood pressure, hypothermia, rapid pulse signs of pleurisy (uncommon), abdominal tenderness with varying degrees of rigidity, and coldness of the extremities

## C. LABORATORY STUDIES IN THE DIAGNOSIS OF DIABETES

*The diagnosis* of diabetes rests finally on laboratory data the most important of which are

1 *Glycosuria*—occurring concomitant with a hyperglycemia
2 *Hyperglycemia*
3 *Special tests* for doubtful cases
   a Effect of a meal containing 100 gm of carbohydrate on the concentration of sugar in the blood
   b Standard glucose tolerance test

c One hour, two dose glucose tolerance test (Exton Rose procedure)

d Intravenous glucose tolerance test

**Glycosuria** The diagnosis of diabetes is made by the appropriate consideration of the presenting symptoms family and past history, physical findings, and especially the laboratory data *Sugar in the urine* is of great diagnostic value because it is recognized so readily by a test applicable as a screening or survey test If everyone would have a specimen of urine, which was voided two to three hours after the biggest meal of the day, tested for sugar, glycosuria could be found in most diabetic patients who were not under treatment * Glycosuria is a signpost pointing to the diagnosis which can be established by finding an excess of sugar in the blood—hyperglycemia

**Hyperglycemia** In the detection of mild diabetes the determination of the blood sugar value two hours after a meal (see p 79) is a much more sensitive test than is a fasting blood sugar value This is important It is important because special tests are most frequently needed in the detection of diabetes when it is present in a mild form The blood sugar value is lowest in the untreated diabetic just before breakfast—this being at the end of the longest period in the twenty four hours without food Normal fasting blood sugar values often occur in the presence of mild diabetes Undoubtedly diabetes often is missed by reliance on fasting blood sugar values in determining the diagnosis It is when the diabetes becomes more severe that the fasting blood sugar is also above normal Repeated fasting (postabsorptive) venous blood sugar values exceeding 130 mg per 100 cc (Folin Wu method)† are clearly indicative of diabetes

*Special Tests for Doubtful Cases*

(a) **Test Meal.** The use of a test meal in detecting diabetes has fallen into relative disuse This is unfortunate because it must be rare indeed that the sugar value in a specimen of blood taken two hours *after a standard meal containing 100 grams of carbohydrate*, does not disclose diabetes if it is present We have, in a small series of diabetic and nondiabetic subjects, compared the results from this test with those from the more exacting, more time consuming and more expensive standard glucose tolerance test and there was no instance in which the results were at variance We

* The American Diabetes Association has endorsed the distribution to the public through pharmacies of a simple equipment—the Selftester—with which anyone can test the urine for sugar *This equipment is prepared by the Ames Company* Inc Elkhart Indiana

† When true venous blood glucose values are employed as determined by the *Somogyi or other method* concentrations in excess of 110 mg per 100 cc fasting and 150 mg after a meal establish the diagnosis of diabetes

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consider this simple test to be more reliable than the one hour, two dose glucose tolerance test, it is inexpensive and it can be readily carried out in a physician's office with a minimum expenditure of time At least as a preliminary study this test has merit and when glucose tolerance tests may be impracticable we recommend it as a satisfactory substitute in many cases in clinical practice

The patient prepares for the test by partaking of a normal diet which will include at least 300 gm of carbohydrate daily for at least three days prior to taking the test meal

The test meal (see Table 11) is taken in place of the regular breakfast and venous blood (5 cc ) for a sugar determination is taken two hours after the meal is finished If the value (venous blood sugar, Folin Wu method) exceeds 170 mg per 100 cc and glycosuria is present it is practically certain that diabetes is the cause If the value is below 130 mg however, it

TABLE 11

TEST MEAL CONTAINING 100 GRAMS OF CARBOHYDRATE

| | | PROTEIN GM | FAT GM | CARBOHYDRATE GM |
|---|---|---|---|---|
| Banana | 155 grams (1 medium) | 1 5 | — | 34 1 |
| Shredded wheat | 30 grams (1 biscuit) | 3 3 | 0 3 | 22 5 |
| Milk | 240 grams (1 cup) | 7 2 | 9 6 | 12 0 |
| Bread (white) | 60 grams (2 slices) | 5 4 | 0 6 | 31 8 |
| Butter | 10 grams (2 teaspoonfuls) | — | 8 5 | |
| Total calories | 612 | 17 4 | 19 0 | 100 4 |

is unlikely that diabetes is present To add to the certainty of the diagnosis a glucose tolerance test (see p 60) may be desirable

A final diagnosis should not be made on the basis of only one determination of the blood sugar Specimens can become misplaced and errors can be made Also, transitory glycosuria and hyperglycemia, nondiabetic in nature, are not uncommon in cases of head injuries, intracranial infections or vascular accidents, thyrotoxicosis, hyperpituitarism, excessive activity of adrenal hormones—medullary and cortical—emotional disturbances, some diseases of the liver, during anesthesia, asphyxia and poisoning from chemicals

Some latitude is permissible in establishing the diagnosis of diabetes in the thyrotoxic patient We allow a moderate degree of hyperglycemia, 20 mg per 100 cc above that of the non thyrotoxic patient, before considering it diagnostic of diabetes Even then, this diagnosis should be tentative, in the borderline cases, until the thyrotoxicosis is corrected and the usual methods of evaluating the diabetes are applicable

**(b) Standard Glucose Tolerance Test.** It is in diabetes mellitus

that gross alterations in carbohydrate tolerance are most frequently observed It is in the detection of this disease in its mildest states that use is made of the fact that normal individuals can ingest considerable quantities of carbohydrate with but trifling changes in the concentration of sugar in

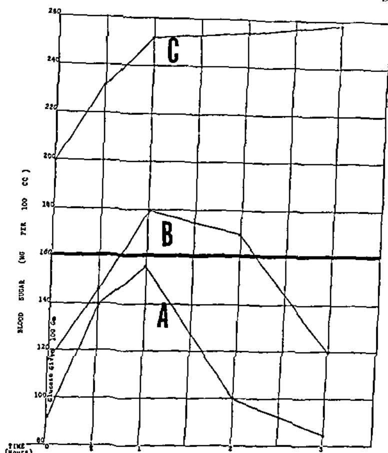



Fig 14 Three glucose tolerance curves. *A* depicts the normal glycemic response to the oral administration of 100 gm of glucose The rise in the blood sugar level is rapid but a normal value is restored in two hours In *B* the glycemic response is slower and normal values are not restored until the third hour as is found in mild diabetes *C* depicts the fasting hyperglycemia and the continued increase in the blood sugar level even at the third hour as seen in severe diabetes. Glycosuria usually occurs when the blood sugar level is maintained for varying periods above 160 mg per 100 cc as depicted by the heavy black line

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level is profoundly len and l made on the
blood *sugar regulating*
The standard gluc is the and, when
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the presence or absence of diabetes The value of this test lies in its diagnostic aid and not as an indicator of the severity of the diabetes If the patient is underweight and has a high fasting blood sugar value the diabetes is almost certain to be severe and in these cases results similar to those depicted in Curve C, Figure 14, would be found, i e, a hyperglycemic fasting blood sugar value with continued increases in the degree of hyperglycemia throughout the three hours subsequent to the oral administration of 100 grams of glucose We wish to emphasize that in clinical practice a confirmed fasting blood sugar value of 130 mg per 100 cc or higher, with glycosuria would establish the diagnosis and make a glucose tolerance test unnecessary The curve (C) is presented as an illustration of the values encountered in such a case and not as a recommendation that a glucose tolerance test be done when the diagnosis is obvious without it Glucose tolerance tests in such cases are needless In spite of this, the practice of performing these tests on patients obviously diabetic is widespread This practice is particularly pernicious in the federal and military hospitals

*Indications* In general the glucose tolerance test is indicated when the diagnosis of diabetes or its exclusion, cannot be clearly made without it Individuals for whom the test is employed will fall into one, or a combination of the following categories, namely, those having

a *History of glycosuria*—applicants for life insurance are the most frequent subjects for a glucose tolerance test under the circumstance of having a history of glycosuria

b *Family history of diabetes*—for many reasons it is important for one with a family history of diabetes to establish the presence or absence of this disorder Contemplation of marriage, the selection of occupation, and the adoption of preventive or palliative measures are examples of these reasons

c *Transitory glycosuria* and *hyperglycemia* during other complications, e g pregnancy, hyperthyroidism hepatitis staphylococcic infections—particularly furuncles and carbuncles—and following a starvation regimen Follow up tolerance tests are of special value in this group

d *Glycosuria without hyperglycemia* as occurs in renal glycosuria, e g, nephrosis and in some cases of pregnancy and of thyrotoxicosis The value of such a study is emphasized when one recalls seeing patients who have been needlessly and ineffectively dieting and taking insulin when the disorder was one of renal glycosuria

*Contraindications* It is important when practicable, to perform this test in the absence of conditions other than a possible diabetes that would influence the tolerance unfavorably For this reason the glucose tolerance test for the detection of diabetes is contraindicated during the course of *infections, hepatic disturbances* and *dietary restrictions* especially a starvation regimen or a low carbohydrate diet or a high fat diet low in carbohydrate content which though they do not alter the true capacity of

pancreatic islet cell function, do exhibit temporary alterations which are adaptations to a reduced demand for insulin (Allen) In patients with thyrotoxicosis an additional 20 *mg of sugar per 100 cc of blood, above* that usually considered as indicative of diabetes, is allowed

The glucose solution occasionally causes nausea This delays absorption and distorts the blood sugar concentration curve, hence, if the curve *does not conform to that for a normal tolerance in the event of nausea,* the test should be repeated after a lapse of seven to ten days Tests done before a week has elapsed may mislead, as in mild diabetes a rapid succession of tests tend to show a progressive improvement in the tolerance for glucose *Also,* active exercise during the course of the test will have a similar effect Contrariwise, prolonged rest in bed tends to reduce the tolerance for glucose and permits slightly higher curves than are obtained when the subjects are ambulatory

*Technic of Standard Glucose Tolerance Test* The patient reports in the morning having had a daily intake of at least 300 gm of carbohydrate for at least three days immediately prior to the test but having had no food since the previous evening The bladder is emptied, a sample of venous blood (5 cc ) for sugar determination is taken and 100 gm of glucose, dissolved in 300 cc of water and flavored with the juice of a lemon, is given by mouth Specimens of blood and urine for sugar determinations are secured one half hour later, and at one, two and three hours

*Interpretation* Two values in the curve depicting the various concentrations of sugar in the blood are of outstanding importance, as it is upon them that the real value of the test depends They are (a) *the fasting blood sugar value* and (b) *the value obtained two hours after the ingestion of 100 gm of glucose (or 1 75 gm per kilogram of body weight in the case of a child)*

FASTING VENOUS BLOOD SUGAR The normal range of the fasting blood sugar concentration is between 70 and 110 mg per 100 cc Values in excess of 130 mg are indicative of diabetes unless proved otherwise

THE TWO HOUR BLOOD SUGAR VALUE The normal individual is able to restore the blood sugar level to 120 mg or lower two hours after the ingestion of the glucose A more liberal interpretation is permissible in the event of one of the complicating conditions (see p 84), which mildly depress the carbohydrate tolerance In these instances two hour values up to 150 mg are considered nondiabetic if the three-hour value is below 120 mg *per 100 cc Such curves are* common in cases of thyrotoxicosis the correction of which restores normal responses to glucose tolerance tests and in so doing justifies the lenient interpretation in such cases

THE PEAK VALUES The maximum concentration of sugar in the blood *normally is found thirty or sixty* minutes after the ingestion of glucose Some authorities believe that if the peak value exceeds 170 mg per 100

cc it is indicative of diabetes We give little heed to the peak of the curve even if it exceeds 200 or 220 mg per 100 cc providing the two hour value is restored to 120 mg or below A blood sugar regulating system which, between the one-hour and two hour intervals, can eradicate such a degree of hyperglycemia is, most probably, not lacking in insulin Unusually high peaks at one half and one hour are more likely to be due to an unusually rapid rate of absorption, as is known to occur in cases of a functioning gastro enterostomy and of thyrotoxicosis

Barring conditioning influences already mentioned a *normal curve* reveals a fasting value below 120 mg and a two hour value at or below 120 mg per 100 cc *Tolerance curves are indicative of diabetes*, if the clinical evaluation is in keeping with the diagnosis, and if the fasting blood sugar exceeds 120 mg and if the two-hour value exceeds 130 mg per 100 cc It is agreed that the fasting blood sugar may be normal, and indeed it usually is, in cases in which the glucose tolerance test is used properly This being the case *the value which is of utmost importance is that obtained at the end of two hours* Indeed, in the majority of cases, the test and interpretation may be simplified and the expense reduced by doing only one blood sugar determination—two hours after the glucose has been taken This is assuming that previous fasting blood sugar values have been normal Barring again, the conditioning influences mentioned on page 84, a two hour value above 130 mg is indicative of diabetes

Glycosuria may influence the type of curve Large quantities of sugar in the urine, occurring concomitantly with blood sugar values on the borderline, would weigh in favor of a diagnosis of diabetes in the belief that had no, or very little glycosuria resulted the concentration of sugar in the blood would have been higher

Urine, collected simultaneously with the collection of each blood sample, permits a study of the relationship of glycosuria to the degree of glycemia as well as some evaluation of the renal threshold

The excretion of glucose in the urine depends upon (a) the concentration of sugar in the arterial blood reaching the glomeruli of the kidneys, (b) the rate at which the glomeruli filter the sugar out of the blood and (c) the rate at which the filtered glucose is reabsorbed by the renal tubules

The renal threshold is usually considered in terms of the concentration of sugar in venous blood which is an unreliable index of the concentration of arterial blood reaching the renal glomeruli for at least several hours after the ingestion of food The varying differences between the arterial and venous blood sugar concentrations during a glucose tolerance test are presented in Figure 15 These differences should be considered in evaluating renal glycosuria if there is to be clear thinking of the physiologic processes in operation

Some authorities, and notably Lawrence,[3] prefer using capillary blood

to venous blood for sugar determinations The former is subject greater range of concentration and is likely to be misleading to experienced with the method

The greater stability of the venous blood sugar values over capillary blood would appear to make the former the more re clinical purposes

*Miscellaneous States Affecting Tolerance Test* The degrees to w bohydrate tolerance is depressed in a multitude of clinical disorde

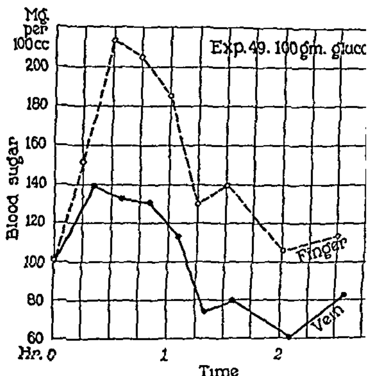



Fig 15 Sugar of venous and finger blood after ingestion of glucose (From G L, J Biol. Chem Vol 55)

slight as to cause no conclusion in differentiating the usual case fro of diabetes These changes are noted in rheumatoid arthritis, senilit plastic diseases, cardiac decompensation arterial hypertension, ne pregnancy, obesity, apoplexy, ulcerative colitis, cirrhosis of the cholecystitis and bronchial asthma It can be gathered from the for remarks that every diabetic patient when suitably studied will exh elevated and prolonged glucose tolerance curve but that every hig prolonged curve is not indicative of diabetes When the results are clusive a subsequent test, or tests, are indicated If employed wise

interpreted in the light of good clinical judgment, glucose tolerance tests will rarely mislead

(c) **The One Hour, Two-Dose Glucose Tolerance Test (Exton Rose)** This test has not been found in our experience, to be as reliable an index of disturbed carbohydrate tolerance as the foregoing standard glucose tolerance test It is convenient in that it is simple to perform requires

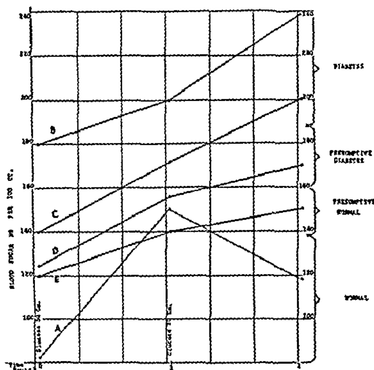



Fig 16 Results of the one hour two-dose glucose tolerance test (Exton Rose procedure)

Note *A* the normal curve the rapid rise and prompt fall of the blood sugar level *B* and *C* characteristic of diabetes with the continued increase in the sugar concentration with fasting values above normal Curve *D* represents presumptive diabetes and curve *E* presumptive normal both are nondiagnostic

fewer venipunctures than the three hour glucose tolerance test and is completed in one hour a desirable feature in office practice The results are dependable if the blood sugar values clearly indicate that diabetes is present *(see curves B and C, Figure 16), or if they clearly signify* a normal tolerance as indicated in curve A It is noted, however, that there is a broad zone in which the interpretation can only indicate a presumptive diagnosis

of diabetes when the blood sugar values are in the upper portion of the zone, or the presumption that diabetes is not present if the values are somewhat lower In practice, a test is needed that will be clearly positive in its indications and especially in those cases in which the one hour test is apt to leave one with a presumptive diagnosis only The high incidence of inconclusiveness which attends the use of this test in doubtful cases has led us to abandon it in preference to the standard *glucose tolerance test* Furthermore, the Exton Rose test has been based on a misconception concerning the underlying physiologic processes which account for the types of curves obtained [4] It is agreed that the maximum rate of absorption of glucose *from the gastro intestinal tract is 0 85 gm per kilo of body weight* per hour or about 60 gm per hour for the average sized man [5] There is evidence that the maximum absorption is carried on at a slower rate than this, namely, 43 gm per hour [6] This being so, a one hour study cannot possibly give an accurate measure of the patient's ability to dispose of 100 gm of glucose, much of which is still in the intestinal tract at the end of this period

Furthermore, it is not the second dose of glucose which causes the blood sugar values to fall in the second half hour of the test but rather the accelerated utilization of sugar by the tissues and cessation of the production of sugar from glycogen by the hepatic processes which are set in motion when the blood sugar is initially increased This mechanism once in action, under normal conditions, continues until the blood sugar is slightly subnormal The blood sugar concentration begins to fall from its peak when the rate of sugar utilization surpasses the rate of absorption from the gastro intestinal tract and this occurs even while maximum absorption is taking place and is not affected by an additional dose of glucose given one half hour after the initial dose Minor changes in the rate of absorption and not necessarily in the rate of utilization, may determine whether the higher concentration of sugar in the blood occurs one half hour or one hour after the administration of the initial dose of glucose This is also true when the standard three hour glucose tolerance test is used but, in this case, the longer period permits a greater degree of correction than is possible in one hour

It is for the foregoing reasons that the Exton Rose glucose tolerance test is *not* recommended for the detection of diabetes in doubtful cases

*Technic* The patient reports before breakfast having had a daily non restricted diet with a carbohydrate intake of at least 300 gm for three days preceding the test One hundred grams of glucose are dissolved in 650 cc of water This is flavored with lemon and divided into two equal parts The test is conducted after an overnight fast

1 The bladder is emptied

2 A sample of venous blood (5 cc ) is taken and immediately there

after one of the portions of glucose in solution (50 gm of glucose) is given by mouth

3 After a thirty minute interval a second sample of blood is taken, a urine specimen secured and the remaining glucose (50 gm ) solution is given

4 After another thirty minute interval specimens of blood and urine are obtained

The sugar concentration in each specimen of blood and the amount of sugar if any in the urine are determined

*Normal Tolerance Curve* 1 The fasting blood sugar level is below 120 mg per 100 cc

2 The one-hour level does not exceed 160 mg per 100 cc

3 The blood sugar level is lower at the end of one hour than at the end of the first half hour

*Tolerance Curves Indicating Diabetes* 1 The fasting blood sugar value may be normal or in excess of 120 mg per 100 cc

2 A continued increase of more than 25 mg in the sugar level during the second half hour

3 A one-hour blood sugar value in excess of 160 mg per 100 cc

(d) **Intravenous Glucose Tolerance Test** This test is not recommended for general clinical use However in the unusual case when it is important to circumvent abnormalities of absorption of glucose from the intestine, such as occurs in thyrotoxicosis, hypothyroidism and gastroenterostomy subjects this test may be of value

*Technic* Glucose 0 5 gm per kilogram of body weight, is given intravenously as a 20 per cent solution in distilled water at a uniform rate over a period of one half hour Blood (5 cc ) is withdrawn for sugar determination before the infusion is begun, at one half hour at one hour and hourly thereafter until four hours have elapsed from the time the infusion was begun

*Interpretation* Normal Result the initial blood sugar level is normal the concentration of sugar in the blood does *not* exceed 0 25 per cent upon completion of the infusion *and the* level thereafter falls steadily, going below the *initial* level at two hours with a return to the pre-injection level or thereabouts between the third and fourth hours

In diabetes the blood sugar does *not* return to normal (below 120 mg per 100 cc ) within two hours of commencing the infusion

## *Differential Diagnosis*

Diabetes may be confused with other disorders which cause glycosuria and hyperglycemia The life of an unconscious patient who has glycosuria and a hyperglycemia as the result of an intracranial hemorrhage may be jeopardized if careful investigation fails to reveal the real illness Should the condition be mistaken for diabetic ketosis and large amounts of insulin be given, the danger is obvious

**Glycosuria.** The presence in the urine of substances which reduce copper in solution to cuprous oxide may be mistaken for glucose These are pentose, lactose, levulose maltose, and rarely galactose, conjugated glycuronates, homogentisic acid, vitamin C and creatinine The recognition of these various factors is dealt with on page 90 Glucose appearing in the urine of a nondiabetic patient is apt to be especially misleading It occurs in *renal glycosuria* and *following intracranial injuries* and in *shock*

**Renal Glycosuria** Glucose appearing in the urine in the presence of a normal blood sugar concentration is known as renal glycosuria, referred to also as 'benign glycosuria" and 'diabetes innocens" Renal glycosuria is a symptomless and innocent condition requiring no treatment It has to do with alterations in the renal threshold for glucose and represents a reduction in the ability of renal tubules to reabsorb sugar which has passed through the glomeruli The blood sugar level above which glycosuria occurs is the so called *renal threshold* for glucose If the venous blood sugar level in the normal individual is increased artificially, glycosuria occurs between

TABLE 12

THE RELATIONSHIP OF THE BLOOD SUGAR LEVEL AND THE SUGAR IN THE URINE IN A CASE OF RENAL GLYCOSURIA

| 1 P M | 1 30 P M | 2 P M | 2 30 P M | 3 P M |
|---|---|---|---|---|
| Blood Sugar Per cent 0 100 | Urine Sugar Per cent 1 5 | Blood Sugar Per cent 0 108 | Urine Sugar Per cent 1 4 | Blood Sugar Per cent 0 098 |

160 and 180 mg per 100 cc In long standing diabetes the renal threshold is often higher, even as high as 250 mg per 100 cc On the other hand, in renal glycosuria glucose appears in the urine without any elevation of the blood sugar above the normal concentration (70 to 110 mg per 100 cc) This innocent disorder occurs in two forms The one in which there is a constant loss of glucose in the urine the quantity of which is not altered by changes in the diet and only with great difficulty by giving insulin, and the other in which there is a temporary lowering of the renal threshold as observed during pregnancy and hyperthyroidism Renal glycosuria is not a forerunner of diabetes Experimentally this condition is produced by giving phlorizin to animals

Importance is attached to renal glycosuria because of the danger of mistaking it for diabetes The combination—diabetes and a low renal threshold for glucose—occurs occasionally

Renal glycosuria is probable if, when the diet is restricted or when insulin is given, there is no decline in the amount of glycosuria Furthermore, from day to day there is *little change in the amount of glycosuria* These inconclusive observations are suggestive but it is only by parallel

examinations of the blood sugar level and the urine that the condition is clearly demonstrated

A simple method of identifying a renal glycosuria is as follows The bladder is emptied and the urine is discarded, 8 oz (240 cc ) of water is given a sample of venous blood is taken thirty minutes later a specimen of urine is obtained and at the end of another thirty minutes blood is again obtained If both blood sugar values are normal (70 to 110 mg per 100 cc ) and if there is a considerable amount of sugar in the urine collected at the midway period the diagnosis of a low renal threshold is confirmed One may carry the test further by securing a second urine specimen and a third blood sugar value as illustrated in Table 12

**Pregnancy and the Renal Threshold** In 10 to 15 per cent of normal pregnant women there is a lowering of the renal threshold for sugar allowing glucose not lactose as is generally supposed to escape in the urine Lactosuria is common during lactation but does not occur during gestation Lactosuria and glycosuria may be observed simultaneously in the same patient The renal threshold for glucose returns to normal after the lactation period has ended

**Hyperthyroidism** In hyperthyroidism it is not unusual to find a lowering of the renal threshold for glucose The problem is not as simple however as that which occurs during pregnancy These patients are apt

frequently is restored to normal by appropriate treatment of the hyperthyroidism Unfortunately this is not always the case

**Nephrosis** The renal threshold for glucose is lowered in nephrosis It is assumed that degenerative changes in the tubular epithelium impair the absorption of glucose from the glomerular filtrate The associated clinical evidences of nephrosis remove any diagnostic difficulties

**Alimentary Glycosuria** It is believed by some that alimentary glycosuria represents a decreased renal threshold for sugar but that the threshold is sufficiently high to prevent continuous glycosuria and that sugar appears in the urine after extra "loads" of carbohydrate This interpretation should be accepted with reserve and a careful study of the individual's carbohydrate tolerance should be made in each instance So-called "alimentary glycosuria" may be due to a reduced renal threshold for sugar or to an increased permeability of the intestinal mucosa for sugar Both causes are innocent It should be suspected however until proven otherwise that the glycosuria is due to diabetes

**Diseases of the Hypophysis** Hyperglycemia and glycosuria indistinguishable from that occurring in uncomplicated diabetes, are common in *acromegaly*

The diabetes which occurs as the result of changes in the hypophysis in the acromegalic patient doubtless has its origin in the excessive activity of the pituitary gland The fact that irreparable changes take place in the pancreas *as a result of these changes has been conclusively* shown experimentally by Young[7]

The important consideration is that acromegalic patients who have hyperglycemia and glycosuria have two disorders, acromegaly and diabetes, and should be treated accordingly

*Pituitary Basophilism* (Cushing's disease) This disease, due to tumor growth of the basophilic cells of the anterior lobe of the pituitary gland also causes hyperglycemia and glycosuria Here also at least two disorders —basophilism and diabetes—coexist The diabetes is doubtless due indirectly to the changes in the hypophysis

**Diseases of the Adrenal Glands.** Hyperglycemia and glycosuria may occur as the result of a *tumor of the adrenal cortex* The diabetes is indistinguishable from chronic diabetes ordinarily seen except that it is cured by removal of the adrenal tumor The clinical signs of tumor of the cortex of the adrenal gland are indistinguishable clinically from those of pituitary *basophilism*

The subcutaneous intramuscular or intravenous injection of epinephrine (adrenalin), an extract of the adrenal medulla, provokes hyperglycemia and may cause glycosuria This is a transitory effect lasting only a matter of minutes It neither causes nor predisposes to diabetes The hyperglycemic *response is due to a liberation of glucose from the liver The same mech*anism, under control of the sympathetic nervous system, operates in shock fear and anger, and permits unusual effort to resist threatened danger

**Intracranial Injury.** Clinically glycosuria and hyperglycemia are common after intracranial trauma This may result from violent accidents *in which the base of the brain is injured and in event of intracranial hem*orrhage as a result of injury or disease of the vascular system, or from injury caused by intracranial tumors and acute infectious processes

Glycosuria of this type is in no way related to diabetes It should be equally clear, however, that a patient having diabetes may suffer an intra*cranial injury and so glycosuria in such cases* should not be dismissed lightly

**Melituria.** Melituria is *a term employed to include all sugars which* may appear in abnormal amounts in the urine Sugar being detected by the usual tests is likely to be *glucose* but it may be levulose, pentose, lactose—*during lactation*—or very rarely galactose maltose, mannoheptulose—following the ingestion of avocados—and sucrose, which does not give a positive reaction for sugar with Benedict's test until hydrolyzed with hydrochloric acid Sucrosuria is to be suspected when a urine free from *albumin* has a specific gravity above 1 035

The clinical significance of the nondiabetic meliturias is, first, the dan

ger that they may be regarded as being due to diabetes with the prospect of a lifetime of treatment second, that a reducing substance in the urine especially glucose in hyperthyroidism and during pregnancy and lactose during lactation, may be taken for granted as being due to the current complication and the possibility of a co-existing diabetes be overlooked, and third, *all meliturias are clinically benign and relatively innocent except the glycosuria due to diabetes* and that uncommonly seen in extensive hepatocellular disease in which case the patient is seriously ill Hence from *the physician s and patient s points of view the problem resolves itself into* a question *Is this sugar in the urine due to diabetes or is it not?* Methods employed in making the diagnosis in problem cases are dealt with on page 77

From the point of view of the scientist it may be important to identify the sugar, especially if it is not glucose and not due to diabetes * Clinically the melituria is of little importance if it is not diabetic in origin and if it does not lead to an incorrect diagnosis

* For more detail on the subject of melituria the reader is referred to the works of Cantarow and Trumper: Clinical Biochemistry 4th Ed W B Saunders Company Philadelphia Also Marble A: Med Clin N Amer p 313 March, 1947

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CHAPTER XII

# Food Requirement

**Introduction.** Every diabetic patient must give special attention to his diet for best results The restrictions are not great In fact, *uniformity of an adequate diet from day to day is the most important feature of the dietary therapy* for diabetes, rather than the severe restrictions as formerly practiced The dietary needs will vary with the conditioning influences such as (a) change in occupation and physical activity, (b) obesity, indicating a reduced caloric intake but with a more liberal diet as the body weight approaches the desired level, and (c) acute complications during which a full quota of calories, protein and carbohydrate with an equally spaced distribution of the diet, throughout the twenty four hours permits better control of the diabetes with insulin

In determining the diet, individualization in terms of so many grams of protein, carbohydrate and fat and the total calories, is the *first* requisite The *second* is filling of the diet prescription in menu form This menu will indicate certain food exchanges (see p 112), which permit a selection from a variety of foods without sacrificing uniformity of values *Thirdly,* the patient is thoroughly trained in the use of household measures, viz, the teaspoon, tablespoon, ounce measure, cup, slice of bread strip of bacon, etc, in accord with the food exchanges permitted in his specific diet

This training we have found, is most effective if done by a dietitian who is especially qualified in simplifying the dietary program, in instructing the patient in the latitude of the selection of foods permitted and in accurately completing the menus Weighing of the food is rarely necessary in the treatment for uncomplicated diabetes

## DIETARY NEEDS

**A. Normal.** Dietary needs are conditioned by age, sex, body weight and occupation The *protein* intake for the normal adult ranges from 60 to 120 grams, the *fat,* 60 to 120 grams, *carbohydrate,* 250 to 400 grams, and *total calories* from 1780 to 3160

**B. *Diabetic.*** The patient whose diabetes is well controlled needs no more and no less food to accomplish the same result than the normal per

son but there is greater urgency to restrict the calories for diabetic patients who are overweight and a modest reduction of the carbohydrate for nearly all diabetics simplifies the control of the diabetes

*Total Calories* The total calories are a most important consideration in planning the diabetic diet One of the fundamental principles in the dietary treatment of the diabetic patient is to avoid overfeeding and for the patients over thirty five years of age the body weight, barring certain

TABLE 13

THE BENEFICIAL EFFECT OF A DIET LOW IN CALORIES IN THE CASE OF AN OBESE DIABETIC PATIENT

(E D female 36 years of age Ht 66 inches Wt 211 pounds)

| DATE | P | F | C. | CAL. | BLOOD SUGAR (MG /100 CC.) | URINE SUGAR | INSULIN (UNITS) | WEIGHT (LB ) |
|---|---|---|---|---|---|---|---|---|
| 1949 | | | | | | | | |
| March 10 | 110 | 95 | 200 | 2100 | | 0-1+ | 155 | 211 |
| 11 | 100 | 33 | 100 | 1100 | 110 | 0 | 110 | |
| 12 | | | | | | 0 | 110 | |
| 13 | | | | | | 0-4+ | 110 | |
| 14 | | | | " | | 0 | 110 | 209 |
| 15 | | | | | | 0 | 110 | |
| 16 | " | | | | | 0 | 110 | |
| 17 | | | | | 81 | 0 | None | |
| 18 | | | | | 143 | 0 | | |
| 19 | | | | | | 0 | | |
| 20 | | " | | | | 0 | | |
| 21 | " | " | " | | | 0 | " | |
| 22 | | | | | | 0 | | |
| Subsequent tests following the patient s discharge from the hospital | | | | | | | | |
| April 1 | 100 | 33 | 100 | 1100 | 160 | 0 | None | 205 |
| April 7 | | | | | 117 | 0 | | 199½ |
| May 5 | | | | | 107 | 0 | | 193 |
| June 16 | | | | | 95 | 0 | | 189 |
| July 21 | | | | | 119 | 0 | " | 187 |
| Sept. 1 | | | " | " | 124 | 0 | | 182 |

complications (p 210) should be brought to 5 to 10 per cent below the standard weight (see Appendix p 265) for his age height and sex Thus thin patients are fattened obese patients are reduced and patients of standard weight are subjected to a minor reduction in weight.

Changes in the total calories have a more far reaching effect on the insulin requirement than have changes in the allowance of carbohydrate (see p 135)

Approximately 75 per cent of adult diabetic patients are overweight when they first seek medical attention because of their diabetes. All authori

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In determining the diet, individualization, in terms of so many grams of protein, carbohydrate and fat and the total calories, is the *first* requisite The *second* is filling of the diet prescription in menu form This menu will indicate certain food exchanges (see p 112), which permit a selection from a variety of foods without sacrificing uniformity of values *Thirdly*, the patient is thoroughly trained in the use of household measures, viz, the teaspoon, tablespoon, ounce measure, cup, slice of bread strip of bacon, etc, in accord with the food exchanges permitted in his specific diet

This training, we have found, is most effective *if done by a dietitian who* is especially qualified in simplifying the dietary program in instructing the patient in the latitude of the selection of foods permitted, and in accurately completing the menus Weighing of the food is rarely necessary in the treatment for uncomplicated diabetes

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| 1949 | | | | | | | | |
| March 10 | 110 | 95 | 200 | 2100 | | 0-1+ | 155 | 211 |
| 11 | 100 | 33 | 100 | 1100 | 110 | 0 | 110 | |
| 12 | | | | | | 0 | 110 | |
| 13 | | | | | | 0-4+ | 110 | |
| 14 | | | | | | 0 | 110 | 209 |
| 15 | | | | | | 0 | 110 | |
| 16 | | | | | | 0 | 110 | |
| 17 | | | | | 81 | 0 | None | |
| 18 | | | | | 143 | 0 | | |
| 19 | | | | | | 0 | | |
| 20 | | | | | | 0 | | |
| 21 | | | | | | 0 | | |
| 22 | | | | | | 0 | | |
| Subsequent tests following the patient s discharge from the hosp tal | | | | | | | | |
| April 1 | 100 | 33 | 100 | 1100 | 160 | 0 | None | 205 |
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| Sept 1 | | | | | 124 | 0 | | 182 |

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Changes in the total calories have a more far reaching effect on the insulin requirement than have changes in the allowance of carbohydrate (see p 135)

Approximately 75 per cent of adult diabetic patients are overweight when they first seek medical attention because of their diabetes All authori

ties on diabetes agree that the *obese diabetic patient* should be reduced, yet the neglect of this important method of controlling the disease and avoiding the use of insulin is widespread The untreated obese diabetic patient has a mild diabetes and, barring complications, control of the disorder can be achieved and maintained by reducing the caloric intake sufficiently to bring about a slow reduction in weight—about two pounds per week Data from the case records of two obese *diabetic patients are presented* in Tables 13 and 22 to illustrate the magnitude of the advantages of reducing the body weight The great saving of insulin and the ease with which the diabetes is controlled are exemplified All will agree that the reduction in weight, in itself, will greatly enhance the life expectancy Patient, E D, although admitted in coma (March 4, 1949) with a blood sugar of 1450 mg per 100 cc, had an inherently mild diabetes, as shown by the ease *with which it was eventually controlled by* restricting the caloric intake and securing a reduction in body weight The prompt elimination of such a large dose of insulin—110 units daily—would be a hazardous undertaking in the case of a thin patient but in the obese subject who is relatively resistant to insulin this can be done without fear in the absence of acute complications For the overweight patient, a diet low in calories (see p 107) will achieve a proper reduction in weight As soon as the diabetes is controlled, the rate of reduction may be cut in half by gradually increasing the caloric intake When the body weight reaches a trifle below the standard level further increases in the diet are made to prevent continued *loss of weight Suitable adjustments are made in the early control phase* and in the eventual long term treatment period to regulate the rate of reduction and to achieve a stationary weight at a desirable level

By using the formula for prescribing the diet as outlined on page 106, it will be found that the individual with a *body weight closely approximating that of the normal* will have a more liberal diet than the overweight patient One dose of insulin daily will probably be needed The *underweight patient* will need a diet adequate to promote a gain in weight and because of the liberal diet and the increasing total body mass and total metabolism, insulin therapy will be essential

*Protein* We have been more liberal with protein in the past few years and have gained the impression that diabetic patients have a better sense of well being when the protein intake exceeds, by a small margin, that ordinarily consumed *by a normal person As a result, it is unusual to prescribe less than 100 grams of protein for the adult male and less than 90 grams for the adult female diabetic*

The diabetic's need for protein is the same as that of the nondiabetic as long as *the diabetes is well controlled* A protein deficit occurs if large amounts of sugar are lost in the urine To correct this feature a liberal allowance of protein, in excess of the normal allowance, and the control

of the diabetes are indicated For the actual estimation of the protein quotas for the individual patient, see page 106

Need for increased protein during growth and in the treatment for certain complications, notably hepatitis, pregnancy, cirrhosis of the liver and nephrosis, is recognized and appropriate amounts are prescribed

*Carbohydrate* The carbohydrate allowance varies with the severity of the diabetes In the case of the overweight patient with mild diabetes insulin therapy can be avoided by the continued restrictions of total calories and carbohydrate These restrictions are relaxed as the body weight decreases and it is not unusual to find these patients tolerating eventually a diet of nearly normal content—carbohydrate, protein, fat and total calories, without hyperglycemia or glycosuria *It is desirable to have the long term diet contain 225 to 300 grams of carbohydrate*

For the underweight diabetic there is ordinarily no escape from insulin therapy and, as small increases in the insulin dosage permit large increases in carbohydrate, liberal quotas of carbohydrate are allowed at once—as much as 200 grams—with additions to 250 and infrequently to 300 grams after the diabetes is controlled

*Fat* Fat is used to make up the calories not provided by the protein and carbohydrate Each gram of protein and of carbohydrate can be considered as providing 4 calories, and each gram of fat 9 calories Hence the calculation of the fat allowance is a simple matter Because of the lipemia and the hypercholesterolemia so commonly associated with diabetes, and the effect of fat on the body weight we prefer to keep the fat content of the diet as low as is practicable It is better to give higher carbohydrate quotas and control the diabetes with insulin when necessary, and to keep the fat content of the diet lower than has formerly been the practice Fat in excess of 100 grams daily is rarely justified It is highly probable that the degenerative changes in the vascular system will be less if the fat intake is kept down to 50 gm daily as advocated by Rabinowitch.[1] A compromise—between 50 and 100 gm —at this stage is justifiable Such allowances will force the carbohydrate and protein quotas upward This is permissible Diets extremely low in fat—less than 40 gm daily—are unpalatable, but with 50 to 75 gm of fat there need be no sacrifice of palatability

**Distribution of Meals** Uniformity of distribution of the diet from day to day reduces the amplitude of the oscillations in the blood sugar concentrations and permits better control of the diabetes than when no two successive breakfasts are alike or no two lunches or no two dinners The diet is adjusted to the individual s needs and the distribution arrived at, as indicated below, is maintained from day to day until new circumstances warrant a change The most common distributions of the diet as illustrated in Figures 17, 18 and 19, are

(a) For the patient having a mild diabetes and *not requiring insulin* the carbohydrate protein and fat are divided equally among the three meals There is no objection to withholding a portion of any meal to be eaten between that mealtime and next, or some from each meal as illustrated in Figure 17, page 109, for a bedtime nourishment

(b) *For the patient taking a single dose of protamine zinc insulin* the outline for three meals (Fig 18) shows that they are equal *but* a portion of the breakfast, usually a glass of milk and three soda crackers—one milk and one bread exchange—is withheld and taken at bedtime (See illustrative diets on pages 125 to 132 ) This practice serves a double purpose First, it means the carbohydrate intake for breakfast is reduced at a time when the action of the morning insulin is not well under way, and second the bedtime nourishment reduces the likelihood of hypoglycemic reactions in the early morning hours and permits, because of this a larger dose of protamine zinc insulin to be given than could be used with safety otherwise

(c) For the patient taking a single dose of *globin* or of *NPH insulin* the diet is divided into three equal meals but, as with protamine zinc insulin, milk and crackers—one milk and one bread exchange—are withheld from breakfast, but in the case of globin insulin (Fig 19) they are taken between 3 and 4 P M In this manner the likelihood of hypoglycemic reactions before supper is guarded against and larger amounts of globin insulin can be given without risk of hypoglycemia than could otherwise be done if this precaution were not taken This is of great practical value since the larger the dose of globin insulin given the more quickly it acts and the longer the blood sugar lowering effect persists Under these circumstances the results obtained with globin insulin more closely duplicate the results obtained with combined regular and protamine zinc insulin therapies

(d) *For the patient taking a dose each of protamine zinc and regular insulin,* separately or mixed with or without a small pre supper dose of regular *insulin, as is necessary in some severe and labile cases,* the diet is divided into three equal meals No food is withheld from breakfast because in this *case the protamine zinc insulin is being supplemented* by the rapidly acting regular insulin It is permissible if the patient wishes, to eat a small portion of *the lunch at 11 A M This practice reduces the chances* of a hypoglycemia—due to the regular insulin—just before lunch Also the same need to prevent a *hypoglycemia in the early morning exists* as in (b) above and to accomplish this a glass of milk and two graham crackers —one milk and one *bread exchange—are taken from* the evening meal (Fig 19) or given, in addition to the prescribed diet at bedtime

The distribution *of the diet in the presence of acute complications* is considered on pages 217 to 221

**Influence of Complications** During *acute complications* particularly infections, which greatly alter the effectiveness of insulin it has been

our practice since 1932 to divide the diet into four equal meals, one given every six hours, or in very rare instances where several hundreds of units of insulin are given in each twenty four hours, the diet is divided into six equal meals and one is given in liquid or soft form, every four hours This feature is dealt with in more detail on pages 217 to 221

This plan of therapy during acute complications has received wide spread adoption It permits the control of the diabetes no matter how severe it may be The control one secures over the diabetes by this measure during acute complications is comparable to the secure control over an automobile which follows when one shifts from high to low gear

Surgical complications, like infections, temporarily increase the severity of the diabetes, and make the administration of insulin necessary This is true even if the diabetes is mild and insulin is not ordinarily needed The diabetic patient who is undergoing a surgical operation, like the patient with an infection, needs a feeding every six hours, each preceded by a dose of regular insulin The details of the management of these patients will be considered in Chapter XVI

The presence of arterial hypertension or of congestive heart failure in a diabetic patient necessitates restriction in the salt intake in addition to the diabetic diet, and the presence of hypercholesterolemia or of xanthoma diabeticorum necessitates restriction of fat and a more liberal use of carbohydrate than is ordinarily indicated

**Standardized Diets.** Convenience is served in the use of standardized diets and for most patients with uncomplicated diabetes, such diets are satisfactory Eleven standard diets are presented in Table 18 and on pages 122 to 132 The diet most closely approximating in total calories, the diet prescription discussed in Chapter XIII is adopted for the individual patient and suitable changes to the more liberal or the more restricted diets are made if indicated by alterations in body weight

Standardized diets are not applicable in dealing with acute complications, such as nephritis with nitrogen retention and duodenal ulcers Diets for such patients must be more highly individualized and made to conform with the diet which experience has shown to be most effective in treatment for existing complications Uniformity of the diet from day to day will permit adequate control of the diabetes, a factor which is usually of no small importance in fortifying the therapy for the complicating disorder

The use of standard diets for patients thoroughly instructed in the flexibilities made possible by using the various food exchanges has simplified greatly the dietetic aspects of the therapy for diabetes

The foregoing plan of dietetic treatment adheres in principle to that advised by Allen and by Joslin though we are more liberal with the protein and carbohydrate quotas but rely greatly on restricted fat and total calories in treating diabetic patients who are overweight

*The more liberal* protein allowance adds remarkably to the 'staying value' of a meal Also, the appetite is more effectively satisfied Because of these advantages that are apparent, and others not so apparent, it is unusual that the so called permanent or long term diet of the adult contains less than 90 grams of protein The carbohydrate allowance is higher than is recommended by Joslin and his associates We favor this increase because it permits a lower fat intake and because it has been proven by Allen and observed many times by us that great increases in carbohydrate are permissible with but little change in the need for insulin, provided the total calories are not increased at the same time—appropriate reductions being made in the fat intake Also, the high incidences of lipemia and hypercholesterolemia and the tendency to degenerative changes in the vascular system in diabetics encourage us to increase the carbohydrate and to decrease the fat to the limits of practicability

**Contrast with Other Diets** *Diets of historical interest are commented* upon in the Chapter on History The diets of today vary greatly We believe the diet prescriptions presented in this book are those which, in general, *are used most widely We tend to give more liberal allowances of* carbohydrate and protein than many but somewhat less carbohydrate than is included in "Free Diets"

In general, three types of diet are considered in present day medical writings

1 The more conservative diet with liberal protein, nearly normal carbohydrate and with the total calories regulated according to the dictates of the body weight This measured diet is aimed, with suitable use of insulin, at restoring physiologic processes, as closely as is practicable, to normal We think of this plan of therapy as the *Physiologic Plan*

2 The high carbohydrate, low fat and low calorie diet advocated by Rabinowitch[1] is standing the test of time and has much in its favor An illustrative diet is as follows Protein, 70 grams, Carbohydrate, 400 grams, and Fat, 50 grams (2330 calories)

3 Free diets as recommended by Stolte[3] are advocated by Tolstoi[4] These are normal diets, not weighed or measured Insulin is used to prevent symptoms but otherwise glycosuria and hyperglycemia are disregarded We believe that this program fosters the maintenance of an unphysiologic state and one which, by permitting hyperglycemia over long periods, predisposes to early degenerative changes Diabetic neuropathies, *increased* susceptibility to tuberculosis and increased hazards during pregnancy are characteristically more prevalent in patients with uncontrolled diabetes It appears inescapable, from accumulating clinical data that a *penalty will eventually be exacted*—a penalty which otherwise might be prevented in some, and postponed in others

**Vitamins and Minerals** *Vitamins* There is no convincing evidence that vitamin *therapy has* a more specific benefit for the diabetic patient

than it has for the nondiabetic There is, however, considerable evidence that diabetic patients require more of the vitamin B complex—especially thiamine, nicotinic acid and riboflavin—than do normal persons One might think that the diet for the diabetic is such that this apparent increased need would be satisfied It is impressive, however, the frequency with which diabetic patients, from middle life on, complain of nondescript aches and pains which subside promptly on thiamine therapy and a recurrence of which is prevented to a large extent by the regular administration of yeast after each meal For these patients we advocate the empirical administration of brewer's yeast with each meal particularly during the winter season when the vitamin intake is likely to be reduced

Peripheral neuritis is a common complication of diabetes which yields to adequate therapy with thiamine, although the response is often a slow one Thiamine, riboflavin and nicotinic acid are known to play essential parts in the enzymatic processes of carbohydrate metabolism and other components of the B complex are possibly just as essential Thiamine deficiency results in a diminution of an essential co carboxylase, diphospho thiamine, and the failure of the carbohydrate to be metabolized past the pyruvic acid phase which follows is detected by finding excessive amounts of pyruvic acid—one of the most active of all the intermediary metabolites —in the blood This abnormal state is intensified by increasing the carbohydrate intake Normal conditions are restored following the administration of thiamine and prolonged control of the diabetes

If it is true that the diabetic patient needs more vitamins than the normal individual as we suspect is the case, the usually recommended minimal intake of vitamins is inadequate It is for this reason and those already presented that we recommend that for adult diabetic patients the vitamin intake should equal that for the normal woman during the latter half of pregnancy, as indicated in Table 14 Additional increases are made for the pregnant diabetic This recommended practice of giving more than the normal requirement of vitamins to our diabetic patients is based largely on the clinical improvement observed as a result of it We shall continue with this measure for this reason and because of the strong impression that by doing so neuropathic changes so common in the diabetic population, may be prevented

Refinements in the industrial processing of foods have reduced their vitamin content This is especially so in the commercial preparation of grains and vegetables and justifies using vitamin-enriched foods and, when advisable, the prescription of supplementary vitamins, as noted above

## TABLE 14

### Recommended Daily Dietary Allowances*
### Revised 1948

*Food and Nutrition Board National Research Council Washington D C*

| | CALORIES | PROTEIN | CAL-CIUM | IRON | VITAMIN A[2] | THIAMINE[3] | RIBOFLAVIN[3] | NIACIN (NICOTINIC ACID)[3] | ASCORBIC ACID | VITAMIN D |
|---|---|---|---|---|---|---|---|---|---|---|
| | | *grams* | *grams* | *mg* | I U | *mg* | *mg* | *mg* | *mg* | I U |
| Man (154 lb 70 kg) | | | | | | | | | | |
| Sedentary | *2400* | 70 | *1 0* | 12[4] | 5000 | 1 2 | *1 8* | 12 | 75 | [illegible] |
| *Physically active* | 3000 | 70 | *1 0* | 12[4] | 5000 | 1 5 | *1 8* | 15 | 75 | [illegible] |
| *With heavy work* | 4500 | 70 | *1 0* | 12[4] | 5000 | *1 8* | *1 8* | *18* | 75 | [illegible] |
| Woman (123 lb 56 kg) | | | | | | | | | | |
| Sedentary | *2000* | 60 | *1 0* | 12 | 5000 | *1 0* | 1 5 | *10* | 70 | |
| Moderately active | *2400* | 60 | *1 0* | 12 | 5000 | 1 2 | *1 5* | 12 | 70 | [illegible] |
| Very active | 3000 | 60 | *1 0* | 12 | 5000 | 1 5 | *1 5* | 15 | 70 | [illegible] |
| Pregnancy (latter half) | *2400*[5] | 85 | 1 5 | 15 | 6000 | *1 5* | 2 5 | *15* | 100 | *400* |
| Lactation | 3000 | 100 | 2 0 | 15 | 8000 | *1 5* | 3 0 | *15* | 150 | *400* |
| Children up to 12 yrs[7] | | | | | | | | | | |
| Under 1 yr[8] | *110/2 2 lb (1 kg)* | 3 5/2 2 lb (1 kg) | 1 0 | 6 | 1500 | 0 4 | 0 6 | 4 | 30 | *400* |
| 1 3 yrs (27 lb 12 kg) | 1200 | 40 | 1 0 | 7 | 2000 | 0 6 | 0 9 | 6 | 35 | 400 |
| 4–6 yrs (42 lb 19 kg) | 1600 | 50 | 1 0 | 8 | 2500 | 0 8 | 1 2 | 8 | 50 | 400 |
| 7–9 yrs (58 lb 26 kg) | 2000 | 60 | 1 0 | 10 | 3500 | 1 0 | 1 5 | 10 | 60 | 400 |
| 10–12 yrs (78 lb 35 kg) | 2500 | 70 | 1 2 | 12 | 4500 | 1 2 | 1 8 | 12 | 75 | 400 |
| Children over 12 yrs[7] | | | | | | | | | | |
| Girls 13 15 yrs (108 lb 49 kg) | 2600 | 80 | 1 3 | 15 | 5000 | 1 3 | 2 0 | 13 | 80 | 400 |
| 16–20 yrs (122 lb 55 kg) | 2400 | 75 | 1 0 | 15 | 5000 | 1 2 | 1 8 | 12 | 80 | 400 |
| Boys 13 15 yrs (108 lb 49 kg) | 3200 | 85 | 1 4 | 15 | 5000 | 1 5 | 2 0 | 15 | 90 | 400 |
| 16–20 yrs (141 lb 64 kg) | 3800 | 100 | 1 4 | 15 | 6000 | *1 7* | 2 5 | *17* | 100 | 400 |

[illegible]

vitamin A

[3] For adults (except pregnant and lactating women) receiving diets supplying 2000 calories or less, [illegible] the allowances of thiamine and niacin may be 1 mg and 10 mg respectively [illegible]

[4] There is evidence that the male adult needs relatively little iron The need will usually be pro[illegible] [illegible]

diet for uncomplicated diabetes The loss of sodium chloride in polyuria may create a craving for salt in the untreated diabetic Also, as ketosis appears and progresses unfavorably, the loss of sodium chloride may reach grave proportions Sodium chloride administered early in the treatment of ketosis is an effective supplementary measure in preventing peripheral vascular collapse (see p 230)

*Calcium* and *potassium* also are present in adequate amounts in the usual diet for the uncomplicated diabetic Great losses of both of these minerals occur in ketosis Decalcification of the bones is common in the elderly diabetic The inclusion of a pint of whole milk or skimmed milk in the daily diet for the adult and a quart of whole milk for the child will prevent calcium and potassium depletion in the absence of complications *Special consideration is given to the potassium intake in ketotic patients* (see p 238) in whom hypopotassemia may be a cause of death

*Iron Deficiency* The absorption of iron is interfered with in cases of achlorhydria—a common occurrence in diabetes in patients past forty five

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above the preceding level The value of 2400 calories represents the allowance for pregnant, sedentary women

Allowances for children are based on the needs for the middle year in each group (as 2 5 8 etc) and are for moderate activity and for average weight at the middle year of the age group

[1] Needs for infants increase from month to month with size and activity The amounts given are for approximately 6 to 8 months *The dietary requirements for some of the nutrients such as protein and calcium are less if derived largely from human milk*

Further recommendations

*Fat* There is available little information concerning the human requirement for fat Fat allowances must be based at present more on food habits than on physiological requirements While a requirement for certain unsaturated fatty acids (the linoleic and arachidonic acids of natural fats) has been amply demonstrated with experimental animals the human need for these same fatty acids is not known *In spite of the paucity of information on this subject there are several factors which make it desirable (1)* that fat be included in the diet to the extent of at least 20 to 25 per cent of the total calories and (2) that the fat intake include essential unsaturated fatty acids to the extent of at least 1 per cent of the total calories At higher levels of caloric expenditure e g for a very active person consuming 4500 calories and for children and for adolescent persons it is desirable that 30 to 35 per cent of the total calories be derived from fat Since foodstuffs such as meat milk cheese nuts etc contribute fat to the diet, it is necessary to use separated or visible fats such as butter oleomargarine, lard or shortening only to supply *one-third to one-half the amounts indicated*

*Water* A suitable allowance of water for adults is 2 5 liters daily in most instances An ordinary standard for diverse persons is one milliliter for each calorie of food Most of this quantity is contained in prepared foods At work or in hot weather requirements may reach 5 to 13 liters daily Water should be allowed ad libitum since sensations of thirst usually serve as adequate guides to intake except for infants and sick persons

*Salt* The needs for salt and for water are closely interrelated A liberal allowance of sodium chloride for the adult is 5 *grams daily* except for some persons who sweat profusely The average normal intake of salt is 10 to 15 grams daily an amount which meets the salt requirements for a water intake up to 4 liters daily When sweating is excessive one additional gram of salt should be consumed for each liter of water in excess of 4 liters daily With heavy work or in hot climates 0 to 30 grams daily may be consumed with meals and in drinking water Even then most persons do not need more salt than usually occurs in prepared foods It has been shown that after acclimatization persons produce sweat that contains only about 0 5 gram to the liter in contrast with a content of 2 to 3 grams for sweat of the unacclimatized person Consequently after acclimatization need for increase of salt beyond that of ordinary food disappears

*Iodine* The requirement for iodine is small probably about 0 002 to 0 004 mg daily for each kilogram of body weight, or a total of 0 15 to 0 30 mg daily for the adult This need is met by the regular use of iodized salt its use is especially important in *adolescence and pregnancy*

*Phosphorus* Available evidence indicates that the phosphorus allowances should be at least equal to those for calcium in the diets of children and of women during the latter part of pregnancy and during lactation In the case of other adults the phosphorus allowances should be approximately 1 5 times those for calcium In general it is safe to assume that if the calcium and protein needs are met through common foods, the phosphorus requirement also will be covered because the common foods richest in calcium and protein are also the best sources of phosphorus

*Copper* The requirement for copper for adults is about 1 to 2 mg daily Infants and children require approximately 0 05 mg for each kilogram of body weight The requirement for copper is approximately one-tenth that for iron A good diet normally will supply sufficient copper

*Vitamin K* The requirement for vitamin K usually is satisfied by any good diet except for the infant in utero and for the first few days after birth Supplemental vitamin K is recommended during the last month of pregnancy When it has not been given in this manner it is recommended for the mother preceding delivery or for the ba[illegible] birth

*Folic acid* Evidence for recog[illegible] acid vitamin Bc L casei factor or vitamin M) as an essent al hu[illegible] qualitative requirement cannot be closely estimated from [illegible] now available

years of age Iron therapy in such cases should be in conjunction with the administration of dilute hydrochloric acid The prescription of ½ dram each of dilute hydrochloric acid and essence of pepsin in a glass of water with each meal plus iron therapy is recommended * Iron depletion associated with achlorhydria in the female during her reproductive years is exceptionally amenable to this combined therapy

Ferrous sulfate 0 2 to 0 3 gm (3 to 5 grains), given orally, three times daily after meals, is effective in many cases of hypochromic anemia without achlorhydria

Choline, or a combination of choline, methionine and inositol (methischol) is administered three or four times daily in cases in which there is enlargement of the liver due to deposits of fat

* For patients who prefer tablets or capsules to liquid medicines, Glutamic acid hydrochloride (Lilly) is available in pulvules for administration with ferrous sulfate Each pulvule of this preparation dispensed as "Acidulin is equivalent to 10 minims of dilute hydrochloric acid U.S P

## REFERENCES


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CHAPTER XIII

# Treatment

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## INTRODUCTION AND DIET

**Introduction.** The treatment of the diabetic patient embraces the control of the physiologic disturbances, in so far as this is practicable, and the guiding and reassuring of the patient in the readjustments which are inevitable with the onset or disclosure of a chronic and, to all intents and purposes, an incurable disease which still carries, to the uninformed, grim stigmata of the past. Reassurance and instruction, especially concerning the diabetes, are important until the patient understands that he will not be starved, that he will be relieved of his symptoms, that he can anticipate a nearly normal life expectancy, that he, himself, will be the helmsman in conducting the treatment—a most reassuring feature when he is qualified to be his own helmsman—and that he will not need to change his occupation, except in rare instances, or give up customary activities.

In short, diabetes, though it is a chronic disease, is controllable and the changes for the patient will be the improved health he will enjoy when treatment gets under way, the adoption of a more uniform plan of eating and exercising from day to day, and the administration of insulin if necessary.

Reassurance, in the early days of his diabetes when he is apt to be needlessly concerned, is an important phase of the preparation of the patient for a lifetime plan of treatment. The psychologic aspect and the physiologic therapy are inseparable and both should be conducted by the internist rather than dividing responsibilities with a psychiatrist.

The treatment for diabetes is not a simple one and, while a certain degree of uniformity exists in the measures employed, no two patients will be treated in identically the same manner. The *objectives* are to provide relief from symptoms; to restore, as nearly as is practicable, a normal physiologic state with freedom from hyperglycemia, glycosuria, hyperlipemia and hypercholesterolemia; to promote normal development physically and mentally, to restore and maintain a high standard of nutrition that will stabilize the body weight at a desirable level, to prevent complications and to reduce the risks to which patients with diabetes are exposed,

e g, infections, surgery, pregnancy and accidents, and to have these patients partake of varied activities which will culminate in an enjoyment of a full life A due regard for the patient as a whole, and not only for his blood sugar level and glycosuria, is important for overall good results

Blood sugar values restored to and maintained within the normal range of fluctuation can have none other than a good result when wisely done It is true that in some cases too strenuous efforts to maintain a normal blood sugar may increase the risk of hypoglycemic reactions However the proper distribution of the diet and the correct selection and combination of insulins, and the exercise of good clinical judgment comprise the methods of solving these problems The glycosuria will subside with proper treatment in most cases and the immediate symptoms of diabetes will be abruptly stopped Certain cases of a peculiarly labile diabetes present special difficulties (see p 256)

The means available for correcting the physiologic disturbances associated with diabetes are (a) dietary management, (b) insulin (c) training of the patient, (d) exercise (e) general care, and (f) miscellaneous measures

Treatment is most effective if the initial phase is carried out in a hospital with the patient on an ambulatory basis A few days—usually four or five—suffice to gain an acquaintance with the characteristics of the individual to have treatment instituted under controlled conditions to evaluate the diabetes and decide on the measures most suited for the individual to observe the initial response to these measures and—of greatest importance—to train the patient in diet management, insulin therapy, testing the urine, and special hygiene

The initial treatment or so called "standardization" conducted at the physician's office is time consuming and is often doomed to failure In the unusual instance, however, and where a properly trained office personnel is available, the efforts may be rewarded with success We know of nothing however, that has such a lasting impression on these patients as the hospital routine and training and we know of no patient who regretted having had this experience

**Diet** Every diabetic patient should be diet conscious He should be aware of the degree of flexibility of the diet permitted in his case and he should understand why there should be quantitative uniformity in diet and regularity of meal time from day to day The objectives of the diet therapy for diabetics are adequate *calories* to restore and maintain *a near* normal body weight, a normal or slightly higher than normal *protein* intake with slight restriction in the *carbohydrate* with sufficient *fat* to provide the calories not provided by the protein and carbohydrate There should be no short changing in minerals nor vitamins and finally, when the optimum diet distribution is decided upon, this plan should be adhered to from day to day To eat a large breakfast and small lunch one day and

the reverse on the next would create undesirable fluctuations of the blood sugar

*Prescription of the Diet for the Diabetic Patient Having No Acute Complication* The initial diet is, at best, a trial diet and alterations are necessary, in most cases, as circumstances change The dietary requirements will vary with sex, age, growth, body build and weight, activities, response to treatment, the severity of the diabetes—and whether the patient needs insulin or not—and complications It is clear that there is no permanently fixed diet for the individual but one which is subject to changes as one or a combination of circumstances dictate However, the aim is to arrive at the diet which will meet all essential requirements and be relatively uniform from day to day In accomplishing this end the following major features are taken into account

(a) Total calories
(b) Protein
(c) Carbohydrate
(d) Fat
(e) Minerals and vitamins (See pp 98 and 99)

In general, overfeeding is avoided, a trifle more protein than formerly prescribed is permitted, the carbohydrate allowance is increased to quotas closely comparable with those of normal diets, and the fat is kept as low as is practicable—below 100 grams in the great majority of cases We share, to a considerable degree, Rabinowitch s respect for a low fat and a more liberal quota of carbohydrate

TOTAL CALORIES The total caloric value of the diet is one of the most important considerations when dealing with the dietary needs of the diabetic patient and changes in the total caloric content of the diet have a far reaching effect in the control of the diabetes These features are exemplified especially in the treatment of the overweight patients who comprise over 70 per cent of the new diabetic patients seen month after month by general practitioners This is a fact that might easily be overlooked when it is realized that most medical writings on the subject of diabetes deal with patients who need insulin The most satisfactorily effective manner of controlling the diabetes in overweight patients is to reduce their weight by means of a reduced caloric intake All authorities are agreed that the obese diabetic should be reduced in weight and yet it is incomprehensible why this efficient means of controlling the disease, and avoiding the use of insulin, is so often entirely neglected The untreated obese diabetic patient has a mild diabetes despite the degree of hyperglycemia and, barring acute complications control of the diabetes can be maintained readily by reducing the caloric intake sufficiently to accomplish a slow reduction in weight

The American Diabetes Association through its Educational Commit

tee, is fostering a uniform method of prescribing diets for diabetic patients With certain modifications, the following plan conforms with their recommendations, except that here we employ measures to reduce the obese patient more rapidly and we allow more protein and more carbohydrate in the diets and hence, less fat

Total Calories (a) To estimate the approximate basic caloric requirement for twenty four hours, multiply the ideal body weight (see Appendix) in pounds* by 10 Add 100 to 200 calories if the patient is a young tall male, deduct 100 to 200 calories if the patient is elderly, short, or female, or *if the patient is obese deduct 200 to 400 calories* (b) For a patient with *ordinary light* activities the diet should usually provide 30 per cent more than the basal calories and, with greater activity, 50 to 75 per cent more than the basal calories (see illustrative diets, p 107)

Example Female patient fifty five years of age, ideal weight 140 pounds, light activity

| | |
|---|---|
| Multiply ideal weight by 10 (140 x 10) | 1400 calories |
| Correction for age and sex, deduct | 100 calories |
| Basal calories | 1300 calories |
| Add 30 per cent | 390 calories |
| Maintenance diet (Total) | 1690 calories |

PROTEIN Multiply the ideal weight in pounds by $\frac{7}{8}$ to determine the protein in grams—children will need higher quotas of protein (Chap XIX)

CARBOHYDRATE The carbohydrate allowance is influenced by the total calories permitted and the severity of the diabetes and, in particular, by whether or not insulin therapy is needed Accordingly, the plan of prescribing this dietary component is as follows

(a) *Carbohydrate allowance—100 to 125 grams—for the obese diabetic receiving a low caloric intake and no insulin* As the diabetes is controlled and the body weight reduced additions are made at relatively long intervals until the diet contains 250 to 300 grams of carbohydrate

(b) *Carbohydrate allowance—250 grams—for the patient who is underweight or normal weight and who needs insulin* Increases to 275 and occasionally to 300 grams are desirable if such a liberal quota does not appreciably increase the difficulty in controlling the diabetes

FAT The balance of the calories not provided by protein and carbohydrate are made up with fat, e g , a diet containing 100 gm protein, 275 gm carbohydrate and 2200 calories will need 77 gm of fat viz ,

* Pounds are used in preference to kilograms This is done without sacrifice of any benefit and because scales for weighing purposes on this continent record weights in pounds and because the computation of kilograms from pounds is avoided.

| | | |
|---|---|---|
| *Protein* | 100 gm. | 400 calories |
| *Carbohydrate* | 275 gm | 1100 calories |
| | Total | 1500 calories |

Balance of calories to be made up with fat
2200 — 1500 = 700 calories 700 — 9 = 77 gm. of fat.

The prescription of the diet may be simplified by merely deciding upon the total calories and adopting the standard diet outlined in Table 18, in which the total calories most nearly approximate that of the prescribed diet

*Illustrative Diet Prescriptions For* A Obese diabetic patient, female, aged fifty five years, actual weight 180 pounds, ideal weight 136 pounds, light activity.

| | |
|---|---|
| Multiply ideal weight by 10 (136 x 10) | 1360 calories |
| Correction for age, sex, degree of obesity, deduct | 400 calories |
| | 960 calories |
| Add 30 per cent for light activity | 288 calories |
| Total | 1248 calories |

As diet No III (p 124) approximates this total caloric value it may be selected without further calculation It will be found to check closely However, the diet prescription may be carried on to include protein and carbohydrate, viz

| | | |
|---|---|---|
| Protein | ⅝ x 136 | 85 gm |
| Carbohydrate | | 130 gm. |

Fat = 1248 — 860 = 388 calories 388 — 9 = 43 gm

B Patient of normal weight, male, age thirty two, actual weight 150 pounds, ideal weight 150 pounds, light activity and receives insulin

| | |
|---|---|
| Multiply ideal weight by 10 (150 x 10) | 1500 calories |
| Correction for age and sex, add | 200 calories |
| | 1700 calories |
| Add 30 per cent for light activity | 510 calories |
| Total | 2210 calories |

The total calories, as calculated, most closely approach that of Diet No VIII (p 129) hence this diet can be prescribed without further calculation Or, if the entire diet prescription is computed it would be as follows

| | | |
|---|---|---|
| Protein | ⅝ x 150 | 93 gm. |
| Carbohydrate (250 to 275 gm) | | 275 gm. |

Fat = 2210 — 1472 = 438 calories 438 — 9 = 48 gm

This difference between the diet calculated in this manner, and diet No VIII, or diet No VII is not sufficient to be of great clinical significance.

C Underweight diabetic patient, female, age eighteen, actual weight 96 pounds, ideal weight 132 pounds, quite active and receives insulin

| | |
|---|---|
| Multiply ideal weight by 10 (132 x 10) | 1320 calories |
| Correction for age and sex deduct | 100 calories |
| | 1220 calories |
| Correction for activity 75 per cent add | 915 calories |
| Total | 2135 calories |

The total calories as estimated most closely approximate those of diet No VII (p 128) This diet may be employed without additional calculation However, individual calculation of the other dietary components would indicate

| | | |
|---|---|---|
| Protein | 6/8 x 132 | 80 gm |
| Carbohydrate | | 260 gm |
| Fat = 2135 — 1360 = 775 calories | 775 — 9 = | 86 gm. |

Adjustments in the diets are made at infrequent intervals after the initial stages of therapy

In the case of the obese patient the rate of the reduction of body weight may be slowed up to a pound or two per month as soon as the diabetes is controlled Suitable increases in the total caloric allowance of the diet are made to secure this end When the body weight reaches the standard level which may require several months, further increases are made to prevent little if any further decreases in weight The return to an obese state, of course, would restore the hazards which accompany it Patients are warned of this

Diets of a low caloric value are employed to reduce weight and to secure the benefits that follow but care should be taken that they do no harm It is especially important that the intake of certain vital food factors should not be reduced beyond the minimal requirements In fact, as indicated on page 99, the diabetic patient may need more of the vitamin B complex than do normal individuals

*Distribution of Meals in Relation to Insulin Therapy* Appropriate distribution of meals permits better control of the diabetes and decreases remarkably the risk of hypoglycemic reactions The accomplishment of these desirable features and the allowance of an adequate diet with great flexibility in the choice of foods comprise our chief reason for adhering to a form of therapy that comes close to physiologic control of the diabetes This is in preference to measures which permit what we consider to be unwarranted degrees of hyperglycemia and glycosuria

On first thought these dietary considerations may appear confusing but they are based on well founded principles and have proved to be most satisfactory Other combinations than those presented may prove to be equally effective but for the sake of simplicity only the programs we have found to be most satisfactory with the respective insulin treatments are presented It will be observed that when the ideal program of insulin therapy (more fully discussed in Chapter XIV) is determined the distribution of the diet becomes automatic In this manner decreases are made in meals *preceding*

the period in which a hyperglycemia is likely and more liberal food intake is permitted preceding periods in which hypoglycemia reactions might otherwise occur

A *No insulin* For the diabetic receiving no insulin a portion is taken from the total diet for a bedtime nourishment In the case of very low caloric diets, e g diet No I (900 calories), this nourishment must necessarily be scant In fact, a glass of skim milk—one milk exchange with the fat omitted—is all that is allowed on the diet referred to But when 1100 calories are permitted, a bedtime nourishment of 1 graham cracker—½ of a bread exchange—is added as indicated in diet No II, page 123

The diet values, after the bedtime nourishment is deducted are divided into three equal meals—for breakfast, lunch and supper, as indicated in

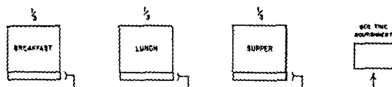



Fig. 17 Depicts the deduction of a nourishment from the total diet for a bedtime nourishment This method of dividing the diet is employed

A When no insulin is needed (see diets I, II III and IV on pages 122 to 125)

B When a combination of regular and protamine zinc insulin—separately or mixed—is given before breakfast with a dose of regular insulin before supper

Figure 17 The deduction of food from the main meals serves to decrease the peaks of demand for insulin and the evening nourishment aids in correcting and in preventing excessive hunger, a favorable feature when the diets are small, as is frequently the case when insulin is not needed *

B. *One dose of protamine zinc insulin daily before breakfast* In this instance a portion of the breakfast—one milk and one bread exchange—is deducted and given at bedtime (Fig 18) The small breakfast is advantageous because of the slowness of the protamine zinc insulin in getting under way and the bedtime nourishment serves to reduce the likelihood of a hypoglycemia during the night when there is still considerable insulin activity

C *One dose of globin insulin daily before breakfast* is the indication for a portion—one milk and one carbohydrate exchange—of the breakfast for consumption between 3 and 4 P M (Fig 18) The action of globin insulin is slow on the "take off" making a small breakfast desirable, and the greatest apparent insulin action being between 3 P M and supper time, a nourishment between 3 and 4 P M reduces or eliminates the likelihood of hypoglycemic reactions before supper

D *One dose each of protamine zinc insulin and globin insulin daily*

* Except when the caloric value of the diet is very low, as in diets No I and No II, the usual values for odd time nourishments are: one milk and one bread exchange, e g, one glass of milk and five saltine crackers.

*before breakfast* calls for a small breakfast with a nourishment between 3 and 4 P M, as a safeguard against a reaction due to *globin insulin*, and a bedtime nourishment *to reduce the risk* of a reaction due to protamine zinc insulin during the night and in the early morning One nourishment —one milk and one carbohydrate exchange—is taken *from the breakfast and the other*, of equal value, is taken from the evening meal as indicated in Figure 19

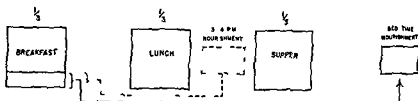



*Fig 18 Illustrates diagrammatically the withdrawal of a nourishment from the* breakfast menu for a bedtime snack when protamine zinc insulin *only* is taken before breakfast The distribution when globin insulin is used is indicated by the broken line

E *One dose of protamine zinc insulin and one dose of regular insulin administered separately or as a mixture* is balanced most satisfactorily with a liberal breakfast—one third of the total diet—a liberal lunch also *one-third, and an evening meal from which a nourishment is deducted for* consumption at bedtime as indicated in Figure 19

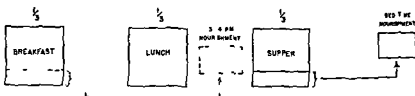



Fig 19 Illustrates diagrammatically the division of the diet

A Solid lines—when *regular insulin* and *protamine zinc insulin* are given before *breakfast.*

B If a dose each ... breakfast the deduction of a ... and 4 P M —indicated by ... hment

... solid and broken lines is also ... or *when regular insulin* is given

The rapid action of regular insulin is the reason for the liberal breakfast The full third of the diet for lunch is advisable as the action of the regular insulin superimposed upon that of the protamine zinc insulin is still quite active well into the afternoon This action has subsided by supper time hence the bedtime nourishment—one milk and one carbohydrate exchange—is taken from the evening meal As in the foregoing instances the bedtime nourishment serves to neutralize the hypoglycemic effect of protamine zinc *insulin between midnight* and breakfast time

F *One dose each of regular insulin and protamine zinc insulin before breakfast, separately or mixed, and one injection of regular insulin before the evening meal* This program, for patients having severe diabetes, indicates, according to principles already dealt with, a liberal breakfast, a liberal lunch, a liberal supper and a bedtime nourishment Hence, as in 'A' (p 109), the bedtime nourishment—a milk and a carbohydrate exchange—is taken from the total diet before it is divided into the three main meals (Fig 17)

G *One dose of NPH insulin* The diet, in the case of a patient taking one dose of NPH insulin daily before breakfast, is divided in a manner that provides a small breakfast, a nourishment between 3 and 4 P M, and a bedtime nourishment as depicted in Figure 19 This distribution is used because of the slowness of the initial action of NPH insulin with the tendency to hyperglycemic values in the mid forenoon unless the breakfast is reduced Some patients tend to have hypoglycemic reactions before supper, hence the 3 to 4 P M nourishment, but others are more prone to reactions during the night and it is for this reason that a bedtime nourishment is prescribed This nourishment is deducted from the evening meal It is well known that if the supper is divided in this manner the influence against a hypoglycemic reaction is much greater than if the same total food were all taken at one meal

H *One dose of NPH insulin to which regular insulin has been added* This has been a very satisfactory mixture of insulins We employ NPH with regular insulin in a proportion of 4 1 almost exclusively and with this mixture the same distribution of the diet as outlined in 'C' and indicated in Figure 19 is used, i e, a portion of breakfast is given between 3 and 4 P M and a portion of the supper at bedtime It is true that, with the rapidly acting regular insulin added, the hyperglycemic tendency during the forenoon is eliminated and accordingly the breakfast need not be reduced However it simplifies matters to take the mid afternoon nourishment from the breakfast when the bedtime nourishment is taken from the supper The risk of hypoglycemic reactions before lunch, because of the reduced breakfast, has not been a problem

## SIMPLIFIED METHOD OF COMPLETING THE MENU FROM A PRESCRIBED DIET—FOR THE PATIENT

The essentials in transposing the information contained in a diet prescription to a menu with the amount of each food for each meal are

1 A prescription for a diet, e g, protein 90 gm, carbohydrate 210 gm, and fat 55 gm (1700 calories)

2 A familiarity with household measuring devices You will need a *standard 8 ounce measuring cup, a teaspoon and tablespoon* Level and not heaped measures are referred to in these pages

3 Special information about foods

a Diets for diabetics are such that no special "diabetic foods"

necessary—the same foods used for the family are best Use in appropriate amounts milk, vegetables, meats, fats and fruits without added sugar (Indeed, some of the diets high in carbohydrate may contain sugar but this is an individual consideration and one to be settled by the physician in charge)

b Seasoning of foods is the same as for the nondiabetic when the following agents are used chopped parsley, mint, garlic, onion, celery, salt, nutmeg, mustard, cinnamon, pepper and other spices, lemon, saccharine and vinegar

c You may use freely, and without reducing your "diet account," coffee, tea, clear broth, bouillon (without fat), gelatin (unsweetened), rennet tablets, pickles (sour, or unsweetened dill), cranberries and rhubarb

4 A working knowledge of the source of food components *Carbohydrate* foods are fruits, cereals, breads, vegetables, etc *Protein* foods are meat, eggs, milk, nuts, etc *Fat* foods are butter, cream, margarine and olive oil

These food components may overlap For instance, while milk is considered a protein food it also contains fat and carbohydrate Also, bread and cereals are carbohydrate foods but contain some protein This overlapping has complicated diet problems in the past but with the adoption of the Exchange System it is now a simple matter to make an appropriate menu from a prescribed diet

5 A familiarity with the Exchange System* which is summarized in Table 15

TABLE 15

COMPOSITION OF FOOD EXCHANGES*

| LIST | FOOD | MEASURES | GM | C | P | F | CAL |
|---|---|---|---|---|---|---|---|
| 1 | Milk Exchanges | ½ pint | 240 | 12 | 8 | 10 | 170 |
| 2a | Vegetable Exchanges | as desired | | | | | |
| 2b | Vegetable Exchanges | ½ cup | 100 | 7 | 2 | | 36 |
| 3 | Fruit Exchanges | varies | | 10 | | | 40 |
| 4 | *Bread Exchanges* | varies | | 15 | 2 | | 68 |
| 5 | Meat Exchanges | 1 oz | 30 | | 7 | 5 | 73 |
| 6 | Fat Exchanges | 1 tsp | 5 | | | 5 | 45 |

* Meal planning has been simplified by the introduction of the "Exchange System" [illegible] American Dietetic As- [illegible]

secured [illegible]
copies with illustrative photographs of average helpings can be purchased

## MILK EXCHANGES—LIST 1

One exchange of milk contains 12 grams Carb [illegible]

Milk is one [illegible]
plan to drink [illegible]
This list shows [illegible]

| Type of Milk | Gm | Amount to Use |
|---|---|---|
| Whole milk (plain or homogenized) | 240 | 1 cup |
| * Skim milk | 240 | 1 cup |
| Evaporated milk | 120 [illegible] | [illegible] |
| Powdered [illegible] | | |

## VEGETABLE EXCHANGES—LIST 2

All vegetables contain sugar but some have more sugar than others The vegetables have been divided into three groups according to the amount of sugar they have
List 2A [illegible]

### VEGETABLE EXCHANGES A

(Contain little Carbohydrate Protein or Calories)

You may [illegible]
[illegible]

| | | |
|---|---|---|
| * Brocc[illegible] | [illegible] Greens | Okra |
| Brussels Sprouts | Chard | * Pepper |
| Cabbage | Collard | Radishes |
| Cauliflower | Dandelion | Sauerkraut |
| Celery | Kale | String Beans young |
| * Chicory | Mustard | Summer Squash |
| Cucumbers | Spinach | * Tomatoes |
| * Escarole | Turnip Greens | * Watercress |
| Eggplant | Lettuce | |

* These vegetables contain significant amounts of vitamin A

### VEGETABLE EXCHANGES B

(Conta[illegible]

These veget[illegible]
use these vege[illegible]
cooked vegetal[illegible]
vegetable

| | |
|---|---|
| Beets | Pumpkin |
| * Carrots | Rutabagas |
| Onions | * Squash, winter |
| Peas green | Turnip |

* These vegetables are rich in vitamin A

You may serve vegetables plain or with part of the meat or fat exchange for seasoning You may wish to use the vegetables milk and meat exchanges in your meal plan together In this way you can make soups stews or other dishes

For salads you may use mayonnaise or French dressing as your fat exchange (For example if you use 1 teaspoon of mayonnaise you would give up 1 teaspoon of butter) Zero salad dressing (recipe page 118) may be used as desired

## FRUIT EXCHANGES—LIST 3

One exchange of fruit contains 10 grams Carbohydrate and 40 Calories

Each exchange of fruit shown below contains about the same amount of sugar Your meal plan will tell you how many exchanges you can have each day You may use your fruit fresh dried cooked canned or frozen as long as no sugar has been added Look at the label on the can or package to be sure it indicates un sweetened or no sugar added

This list shows the different amounts of fruits to use for one fruit exchange

| | *Meas* | *Gm* |
|---|---|---|
| Apple | 1 small (2 diam ) | 80 |
| Applesauce | ½ cup | 100 |
| Apricots fresh | 2 medium | 100 |
| Apricots dried | 4 halves | 20 |
| Banana | ½ small | 50 |
| Berries Straw * Rasp Black | 1 cup | 150 |
| * Blueberries | ⅔ cup | 100 |
| Cantaloupe | ¼ (6 diam ) | 200 |
| Cherries | 10 large | 75 |
| Dates | 2 | 15 |
| Figs fresh | 2 large | 50 |
| Figs dried | 1 small | 15 |
| * Grapefruit | ½ small | 125 |
| * Grapefruit Juice | ½ cup | 100 |
| Grapes | 12 | 75 |
| Grape Juice | ¼ cup | 60 |
| Honeydew Melon | ⅛ (7 diam ) | 150 |
| Mango | ½ small | 70 |
| * Orange | 1 small | 100 |
| * Orange Juice | ½ cup | 100 |
| Papaya | ⅓ medium | 100 |
| Peach | 1 medium | 100 |
| Pear | 1 small | 100 |
| Pineapple | ½ cup | 80 |
| Pineapple Juice | ⅓ cup | 80 |
| Plums | 2 medium | 100 |
| Prunes dried | 2 medium | 25 |
| Raisins | 2 Tbsp | 15 |
| * Tangerine | 1 large | 100 |
| Watermelon | 1 cup | 175 |

For variety you can serve fruit as a salad or with unsweetened gelatin as a dessert

* These fruits are rich sources of Vitamin C use at least one serving each day

## BREAD EXCHANGES—LIST 4

One bread exchange contains 15 grams Carbohydrate 2 grams Protein and 70 Calories

For each bread exchange called for on your meal plan choose any one item on the list below

For example

½ cup cooked cereal will give you 1 Bread Exchange

1 slice bread and 1 small potato will give you 2 Bread Exchanges

1 slice bread and ½ cup cooked rice and ⅓ cup corn will give you 3 Bread Ex changes

This list shows the different amounts of foods to use for one bread exchange

| | Meas | Gm |
|---|---|---|
| Bread | 1 slice | 25 |
| Biscuit, Roll | 1 (2 diam) | 35 |
| Muffin | 1 (2 diam) | 35 |
| Cornbread | 1 (1½ cube) | 35 |
| Flour | 2½ Tbsp | 20 |
| Cereal cooked | ½ cup | 100 |
| Cereal dry (flake & puffed) | ¾ cup | 20 |
| Rice Grits cooked | ½ cup | 100 |
| Spaghetti Noodles etc cooked | ½ cup | 100 |
| Crackers graham (2½ sq) | 2 | 20 |
| Oyster | 20 (½ cup) | 20 |
| Saltines (2 sq) | 5 | 20 |
| Soda (2½ sq) | 3 | 20 |
| Round thin (1½ diam) | 6–8 | 20 |
| Vegetables | | |
| Beans & Peas dried cooked (lima navy split pea cowpeas etc) | ½ cup | 90 |
| Baked Beans no pork | ¼ cup | 50 |
| Corn | ⅓ cup | 80 |
| Parsnips | ⅔ cup | 125 |
| Potatoes white baked boiled | 1 (2 diam) | 100 |
| Potatoes white mashed | ½ cup | 100 |
| Potatoes sweet or Yams | ¼ cup | 50 |
| Sponge Cake plain | 1 (1½ cube) | 25 |
| Ice Cream (Omit 2 fat exchanges) | ⅙ pint | 70 |

B

white crackers rice or spaghetti that do not have the vitamins added

## MEAT EXCHANGES—LIST 5

One meat exchange contains 7 grams Protein 5 grams Fat and 75 Calories

You may have any kind of meat you wish Cheese eggs and peanut butter can be taken in place of meat for variety

For each meat exchange called for on your meal plan choose any one item on the list below

For example

1 Egg will give you 1 Meat Exchange

1 ounce Cheese and 1 ounce Ham will give you 2 Meat Exchanges

1 Egg and ¼ cup Cottage Cheese and 1 slice Bologna will give you 3 Meat Exchanges

This list shows the different amounts of foods to use for one meat exchange

| | Meas | Gm |
|---|---|---|
| Meat & Poultry (med fat) (beef lamb pork liver chicken etc) | 1 oz | 30 |
| Cold Cuts (4½ sq ⅛ thick) | 1 slice | 45 |
| Frankfurter | 1 (8–9/lb) | 50 |
| Fish Cod Mackerel etc | 1 oz | 30 |
| Salmon Tuna Crab | ¼ cup | 30 |
| Oysters Shrimp Clams | 5 small | 45 |
| Sardines | 3 medium | 30 |
| Cheese cheddar American | 1 oz | 30 |
| Cottage | ¼ cup | 45 |
| Egg | 1 | 50 |
| Peanut Butter | 2 Tbsp. | 30 |

## FAT EXCHANGES—LIST 6

One fat exchange contains 5 grams Fat and 45 Calories

All fat foods are high in calories Too much fat or too much of any food may cause you to gain weight A person with diabetes should try to reach his ideal weight If he weighs too much his diabetes will be harder to control

Use the foods on this list only as allowed on your meal plan

You may use your fat exchanges in preparing such foods as vegetables and meats For example if you use a teaspoon of fat to fry an egg give up one fat exchange

For each fat exchange called for on your meal plan choose any one item on the list below

For example

1 teaspoon butter will give you 1 Fat Exchange

1 teaspoon margarine and 1 slice bacon will give you 2 Fat Exchanges

This list shows the different foods to use for one fat exchange

| | *Meas* | *Gm* |
|---|---|---|
| *Butter or Margarine* | *1 tsp* | *5* |
| Bacon crisp | 1 slice | 10 |
| Cream light 20% | 2 Tbsp | 30 |
| Cream heavy 40% | 1 Tbsp | 15 |
| Cream Cheese | 1 Tbsp | 15 |
| *French Dressing* | *1 Tbsp* | 15 |
| Mayonnaise | 1 tsp | 5 |
| Oil or Cooking Fat | 1 tsp | 5 |
| Nuts | 6 small | 10 |
| Olives | 5 small | 50 |
| Avocado | ⅛ (4 diam) | 25 |

6 A familiarity with the means and advantages of a varied dietary The recipes included in the patients' pamphlet as prepared by the American Diabetes and American Dietetic Associations are included in the prospect that they will be helpful as examples in this respect

### RECIPES

#### LEMON GELATIN

(May be used in any amount)

1 teaspoon unflavored gelatin
2 tablespoons cold water
1 tablespoon lemon juice
½ cup water

stand 10 minutes at room
ou wish you may
n juice and ½ cup
½ cup coffee in
place of ½ cup water

ORANGE GELATIN 1 Serving *equals* 1 Fruit from List 3
Use ½ cup orange juice in place of water in recipe for lemon gelatin

PINEAPPLE GELATIN 1 Serving *equals* 1 Fruit from List 3

| | |
|---|---|
| 1 teaspoon unflavored gelatin | 1 tablespoon lemon juice |
| ¼ cup cold water | ½ cup pineapple juice |

FRUIT GELATIN—I 1 Serving *equals* 1 Fruit from List 3
One serving of any fruit from List 3 may be added to lemon gelatin such as ½ small banana.

FRUIT GELATIN—II 1 Serving *equals* 2 Fruits from List 3
One serving of any fruit from List 3 may be added to orange or pineapple gelatin

## FRUIT ICE

1 Serving *equals* 1 Fruit from List 3

| | |
|---|---|
| ½ cup orange juice or ½ cup pineapple juice | 1 egg white |
| 1 tablespoon lemon juice | ½ cup water |

Combine fruit juice and water and freeze Stir mixture often while freezing When almost hard fold in one stiffly beaten egg white

## FRESH FRUIT CUP

(1 Serving *equals* 1 Fruit from List 3)

Any fruits in List 3 may be combined to make a fruit cup ½ cup of mixed fruits equals 1 serving

Example

Orange Grapefruit Pineapple
Apple Grapefruit Strawberries
Peach Orange Blackberries
Grapes Orange Melon
Melon Grapefruit, Banana

## CANNING FRUIT WITHOUT SUGAR

(1 Serving *equals* 1 Fruit from List 3)

Any fruit—peaches pears etc may be canned at home by following the usual directions for canning except that you omit the sugar Can fruit in its own juice with enough water added to fill the jar You will find directions in any cook book for the amount of time to steam the fruit The fruit will keep all right if the can is *properly sealed*

## BAKED CUSTARD

1 Serving *equals* ½ cup Milk and 1 Meat Exchange)

| | | |
|---|---|---|
| 1 egg | Few grains salt | ⅛ teaspoon vanilla |
| ½ cup milk | | Sprinkle of nutmeg |

Beat the egg slightly stir in milk salt and vanilla If you wish add ¼ grain saccharin to flavor Pour into a custard cup and sprinkle with nutmeg Set in pan of hot water and bake in a moderate oven (350°) for about 45 minutes

Other flavors such as almond lemon orange or maple may be used in place of vanilla

## CHEESE FONDUE

(1 Serving *equals* 1 Bread Exchange and 2 Meat Exchanges and 1 cup Milk)

| | |
|---|---|
| 1 egg | 1 slice bread cubed |
| 1 cup milk | ¼ cup cheese diced (1 oz) |

Salt pepper chopped parsley and onion

Beat the egg add milk bread cheese and seasoning Bake in a moderate oven (350°) until firm in the center about 20 or 30 minutes

In place of cheese ¼ cup (1 oz) of chopped ham chicken tuna fish or salmon may be used

VEGETABLE SOUP

(1 Serving *equals* 1 Vegetable from List 2B)

1 cup meat stock *or* bouillon cube and 1 cup water
½ cup mixed vegetables carrots, peas
½ small onion, chopped
¼ cup cabbage shredded
1 stalk celery, diced
¼ cup tomato juice
Salt and pepper

Prepare vegetables and add to broth Boil together until vegetables are just tender about 20 minutes

POTATO SALAD A

(1 Serving *equals* 1 Bread Exchange)

½ cup cooked potato diced
1 or 2 tablespoons Zero salad dressing
Salt, pepper, chopped onion celery, parsley, green pepper, as desired
Combine ingredients and serve

POTATO SALAD B

(1 Serving *equals* 1 Fat Exchange and 1 Bread Exchange)

Use same recipe as Potato Salad A except that 1 teaspoon of mayonnaise may be used in place of Zero salad dressing

POTATO SALAD C

(1 Serving *equals* 1 Bread Exchange and 1 Meat Exchange and 1 Fat Exchange *if desired*)

1 hard cooked egg, sliced, may be added to recipe for Potato Salad A or B

¼ cup (1 oz ) diced ham bologna or frankfurt, or 5 small shrimp may be used in place of egg

ZERO SALAD DRESSING

(May be used in any amount)

½ cup tomato juice
2 tablespoons lemon juice or vinegar
1 tablespoon onion finely chopped
Salt and pepper

Chopped parsley or green pepper horseradish, or mustard etc , may be added if desired

Combine ingredients in a jar with a tightly fitted top Shake well before using

MEAT STEW

(1 Serving *equals* 2 or 3 Meat Exchanges and 1 Bread Exchange and 1 Serving Vegetable from List 2B and 1 Fat Exchange)

1 teaspoon fat
1½ cup mixed vegetables list 2B (carrots, peas onions)
2 or 3 oz meat cubed
1 small potato
Salt and pepper to taste

BAKED CHICKEN AND RICE

(1 Serving *equals* 1 Bread Exchange and 1 or 2 Meat Exchanges)

½ cup cooked rice
¼ or ½ cup diced chicken (1 or 2 oz )
¼ cup clear broth
Salt and pepper

Chopped parsley, onions, celery, mushrooms green pepper, pimento *or* tomatoes may be added for variety, if desired

Combine the above ingredients and place in dish Bake in a moderate oven until brown

In place of rice you may use noodles or spaghetti For the chicken you may use any type of meat or fish, such as, lamb, ham, tuna or shrimp

FISH CHOWDER

(1 Serving *equals* 1 Fat Exchange and 1 Bread Exchange and 1 or 2 Meat Exchanges and 1 cup Milk)

| | |
|---|---|
| 1 teaspoon fat | ¼ or ½ cup cooked fish (1 or 2 oz) |
| ½ small onion chopped | 1 cup milk |
| 1 small potato sliced | Salt and pepper |

Cook fish in salted water Melt fat in saucepan brown the onion Add cooked fish sliced potato ½ cup water in which fish was cooked Cover and cook for 15 minutes until potatoes are tender Add milk and seasonings

ITALIAN SPAGHETTI

(1 Serving *equals* 1 or 2 Meat Exchanges and 1 or 2 Bread Exchanges and 1 Fat Exchange)

| | |
|---|---|
| 1 teaspoon fat | Salt pepper |
| ½ small onion chopped | ½ cup tomatoes |
| 2 tablespoons tomato paste | 1 or 2 oz hamburg |
| ¼ cup water | ½ cup cooked spaghetti |

Brown the onion hamburg and fat Add the tomato paste water and tomatoes Allow *to simmer* gently one or more hours If needed add more water Serve on ½ or 1 cup cooked spaghetti 1 or 2 teaspoons grated cheese may be used

MACARONI AND CHEESE

(1 Serving *equals* 1 Bread Exchange and 1 or 2 Meat Exchanges and ¼ cup Milk)

| | |
|---|---|
| ½ cup cooked macaroni | ¼ cup milk |
| ¼ or ½ cup diced cheese (1 or 2 oz) | Salt pepper dash of mustard |

Cook cheese and milk together in *double boiler* until smooth Add macaroni and mix well Bake in moderate oven about 20 minutes or until brown

In place of macaroni you may use ½ cup cooked rice noodles or spaghetti

MIXED VEGETABLE SALAD

(May be used in any amount)

Any combination of vegetables from List 2A may be used such as

1 Lettuce cucumber celery green pepper
2 Chicory tomato radish

7 Lettuce raw spinach radish

Salad may be combined with Zero Salad Dressing French Dressing or Mayonnaise depending upon fat allowed in your meal plan

## MAKING THE MENU

*Illustration* Diet Prescription Protein 90 gm carbohydrate 210 gm fat 55 gm and 1700 calories (Standard diet No V, p 126)

Step I Divide the day's protein, fat and carbohydrate allowances into approximately three equal meals * Example—

| | |
|---|---|
| Protein | 90 ÷ 3 = 30 gm |
| Fat | 55 ÷ 3 = 18 to 19 gm |
| Carbohydrate | 210 ÷ 3 = 70 gm |

Step II Plan the menu for each meal

Example (a) List the foods desired for breakfast as designated in column A Table 16

* Unequal distribution of the diet is often indicated This is discussed on pages 108 and 111 and illustrated in the standard diets on pages 122 to 132

(b) Insert the exchange from which each food is taken as in column B and for convenience add the list number of each as in column C

TABLE 16

ILLUSTRATIVE MENU FOR BREAKFAST

| A | B | C | D | E | |
|---|---|---|---|---|---|
| Eggs | Meat exchange | list #5 | 2 | 2 | eggs |
| Bread | Bread exchange | list #4 | 3 | 3 slices | bread |
| Butter | Fat exchange | list #6 | 1 | 1 tsp | butter |
| Milk | Milk exchange | list #1 | 1 | 1 cup | milk |
| Fruit | Fruit exchange | list #3 | 1½ | 1½ serving | fruit |

Step III Adjust the amounts (the number of exchanges) until they fill the total for each dietary component as in column D This procedure is expedited by completing the *carbohydrate* quota first, then the *protein*, and lastly the *fat* The foods and amount of each which are selected to use up the exchanges allowed are listed in column E The completed menu is presented in Table 17

TABLE 17

ILLUSTRATION OF COMPLETED MENU

| | NO EXCHANGES | HOUSEHOLD MEASURE | WEIGHT GRAMS | P | F | C |
|---|---|---|---|---|---|---|
| *Breakfast* | | | | | | |
| Meat | 2 | 2 eggs | | 14 | 10 | — |
| Bread | 3 | 3 sl | 75 | 6 | — | 45 |
| Fat | 1 | 1 tsp | 5 | — | 5 | — |
| Milk skim | 1 | 1 c | 240 | 8 | — | 12 |
| Fruit | 1½ | 1½ serv | See list 3 | — | — | 15 |
| | | | | 28 | 15 | 72 |
| *Lunch (or supper)* | | | | | | |
| Meat | 2 | 2 oz | 60 | 14 | 10 | — |
| Bread | 3 | 3 sl | 75 | 6 | — | 45 |
| Fat | 2 | 2 tsp | 10 | — | 10 | — |
| Vegetable | 2A | 1 serv | 100 | — | — | — |
| Vegetable | 2B | 1 serv | 100 | 2 | — | 7 |
| Milk skim | 1 | 1 c | 240 | 8 | — | 12 |
| Fruit | 1 | 1 serv | See list 3 | — | — | 10 |
| | | | | 30 | 20 | 74 |
| *Evening or (Main Meal)* | | | | | | |
| Meat | 3 | 3 oz | 90 | 21 | 15 | — |
| Bread | 3 | 3 sl | 75 | 6 | — | 45 |
| Fat | 1 | 1 tsp | 5 | — | 5 | — |
| Vegetable | 2A | 1 serv | 100 | — | — | — |
| Vegetable | 2B | 1 serv | 100 | 2 | — | 7 |
| Fruit | 1½ | 1½ serv | See list 3 | — | — | 15 |
| | | | | 29 | 20 | 67 |
| | | Day's Total | | 87 | 55 | 213 |

## STANDARD DIETS

Standard diets as indicated in Table 18, aid greatly in simplifying the treatment of diabetic patients For uncomplicated diabetes they serve admirably but they should not be used at the expense of more intensive individualization which may be highly desirable during the course of complicating diseases e g duodenal ulcer, hepatitis, etc The diet prescription may be suitable in such cases but the food components and the distribution of the diet are altered to meet the individual's needs and appropriate changes are made in the insulin therapy to maintain good control of the diabetes

Maximum usefulness of the standard diets will be obtained (a) when the prescription for the diet is arrived at as outlined on pages 106 to 108 and (b) when full advantage is taken of the flexibilities permitted by the various food exchanges In the illustrative standard diets (pages 122 to 132) a "food exchange" column is included to simplify the substitution of suitable foods for those indicated in the sample menu

TABLE 18

Standard Diet Prescriptions

| | PROTEIN | CARBOHYDRATE | FAT | CALORIES |
|---|---|---|---|---|
| I | 75 | 100 | 22 | 900 |
| II | 80 | 120 | 33 | 1100 |
| III | 85 | 130 | 49 | 1300 |
| IV | 90 | 180 | 47 | 1500 |
| V | 90 | 210 | 55 | 1700 |
| VI | 90 | 230 | 69 | 1900 |
| VII | 95 | 260 | 75 | 2100 |
| VIII | 95 | 280 | 89 | 2300 |
| IX | 100 | 300 | 100 | 2500 |
| X | 110 | 320 | 109 | 2700 |
| XI | 120 | 335 | 120 | 2900 |

Eleven standard diet prescriptions are filed in this table Diets III IV V and VI are suitable for the initial treatment in the majority of cases and for the more permanent programs diets VI VII and VIII suffice for the majority of the adult patients It will be noted that (a) the protein and carbohydrate allowances in the more permanent diets are more liberal than formerly used and (b) the fat content is kept below 100 grams except in the three high caloric diets

The standard diets Nos I to IV inclusive—providing 900 1100, 1300 and 1500 calories respectively—are used in the treatment of overweight patients having mild diabetes These patients do not need insulin and they are at liberty to save any part of any meal to be taken between meals or at bedtime if desired It is inadvisable on the other hand to take only two big meals in the day or two very small meals and one large meal

The more liberal diets—from 1700 to 2900 calories—are commonly used by patients taking insulin in which case there are specific indications for a distribution of the diet which gives maximum advantage to the respective insulin therapy This feature has been dealt with already in detail (p 103)

DIET NO I—900 CALORIES
Protein 75 gm , Fat 22 gm Carb 100 gm
Division of diet approximately ⅓ for each meal with a bedtime nourishment

| NO EXCHANGES | FOOD EXCHANGE | LIST NO | SAMPLE MENU | HOUSEHOLD MEAS | WT GM | P | F | C | CAL. |
|---|---|---|---|---|---|---|---|---|---|
| Breakfast | | | | | | | | | |
| 2 | Meat | 5 | Eggs | 2 | | 14 | 10 | — | 146 |
| 1 | Bread | 4 | Bread | 1 sl | 25 | 2 | — | 15 | 68 |
| 1 | Fruit | 3 | Orange | 1 sm | 100 | — | — | 10 | 40 |
| ¼ | Milk | 1 | Skim milk | ¼ c | 60 | 2 | — | 3 | 20 |
| | | | | Total | | 18 | 10 | 28 | 274 |
| Lunch (or Supper) | | | | | | | | | |
| 3 | Meat | 5 | *Roast beef (lean) | 3 oz | 90 | 21 | 9 | — | 165 |
| 1 | Bread* | 4 | Bread | 1 sl | 25 | 2 | — | 15 | 68 |
| 1 | Vegetable | 2A | String beans, young | ½ c | 100 | — | — | — | — |
| ½ | Milk | 1 | Skim milk | ½ c | 120 | 4 | — | 6 | 40 |
| 1 | Fruit | 3 | Peach | 1 med | 100 | — | — | 10 | 40 |
| | | | | Total | | 27 | 9 | 31 | 313 |
| Dinner (or Main Meal) | | | | | | | | | |
| 2 | Meat | 5 | Broiled liver | 2 oz | 60 | 14 | 6 | — | 110 |
| ½ | Bread | 4 | Bread | ½ sl | 13 | 1 | — | 8 | 36 |
| 1 | Vegetable | 2A | Lettuce and cucumber | | 100 | — | — | — | — |
| 1 | Milk | 1 | Skim milk | 1 c | 240 | 8 | — | 12 | 80 |
| 1 | Fruit | 3 | Strawberries | 1 c | 150 | — | — | 10 | 40 |
| | | | | Total | | 23 | 6 | 30 | 266 |
| Nourishment | | | | | | | | | |
| 1 | Milk | 1 | Skim milk | 1 c | 240 | 8 | — | 12 | 80 |
| | | | | Day's total | | 76 | 25 | 101 | 933 |

* Visible fat removed

Note sm—small, med—medium, lg—large, oz—ounce, tbsp—tablespoon tsp—teaspoon, c—cup, sl—slice

This low calorie diet (900 calories) is used as a temporary measure to permit a reduction in the weight of the obese diabetic patient A nourishment has been taken from the total diet for use at bedtime Ordinarily patients receiving this diet are not taking insulin

DIET NO II—1100 CALORIES

Protein 80 gm Fat 33 gm Carb 120 gm

Division of diet approximately ⅓ for each meal with a bedtime nourishment

| NO EXCHANGES | FOOD EXCHANGE | LIST NO | SAMPLE MENU | HOUSEHOLD MEAS | WT GM | P | F | C | CAL |
|---|---|---|---|---|---|---|---|---|---|
| Breakfast | | | | | | | | | |
| 2 | Meat | 5 | Eggs | 2 | | 14 | 10 | — | 146 |
| 1 | Bread | 4 | Bread | 1 sl | 25 | 2 | — | 15 | 68 |
| ¾ | Milk | 1 | Skim milk | ¾ c | 180 | 6 | — | 9 | 60 |
| 1 | Fruit | 3 | Cantaloupe | ¼ med | 200 | — | — | 10 | 40 |
| | | | | Total | | 22 | 10 | 34 | 314 |
| Lunch (or Supper) | | | | | | | | | |
| 2 | Meat | 5 | Cottage Cheese | ½ c | 90 | 14 | 10 | — | 146 |
| 1 | Vegetable | 2A | Tomato and lettuce | 1 | 100 | — | — | — | — |
| 1 | Bread | 4 | Muffin | 1 | 35 | 2 | — | 15 | 68 |
| ¾ | Milk | 1 | Skim milk | ¾ c | 180 | 6 | — | 9 | 60 |
| 1 | Fruit | 3 | Applesauce | ½ c | 100 | — | — | 10 | 40 |
| | | | | Total | | 22 | 10 | 34 | 314 |
| Dinner (or Main Meal) | | | | | | | | | |
| 3 | Meat | 5 | Roast Lamb | 3 oz | 90 | 21 | 15 | — | 219 |
| 1 | Vegetable | 2A | Spinach | ½ c | 100 | — | — | — | — |
| 1 | Vegetable | 2B | Pickled beets | ½ c | 100 | 2 | — | 7 | 36 |
| 1 | Bread | 4 | Bread | 1 sl | 25 | 2 | — | 15 | 68 |
| 1 | Fruit | 3 | Apricots | 2 med | 100 | — | — | 10 | 40 |
| | | | | Total | | 25 | 15 | 32 | 363 |
| Nourishment | | | | | | | | | |
| 1 | Milk | 1 | Skim milk | 1 c | 240 | 8 | — | 12 | 80 |
| ½ | Bread | 4 | Graham cracker | 1 | 10 | 1 | — | 8 | 36 |
| | | | | Total | | 9 | — | 20 | 116 |
| | | | | Day's Total | | 78 | 35 | 120 | 1107 |

For key to abbreviations see footnote, p 122

As is the case of the first diet (900 calories) this diet—1100 calories—is also employed to reduce body weight of obese diabetic patients A nourishment, deducted from the total diet is taken at bedtime. Ordinarily this diet is not supplemented with insulin therapy

Diet No III—1300 Calories
Protein 85 gm , Fat 49 gm Carb 130 gm
Division of diet approximately ⅓ for each meal with a bedtime nourishment

| No Exchanges | Food Exchange | List No | Sample Menu | Household Meas | Wt Gm | P | F | C | Cal |
|---|---|---|---|---|---|---|---|---|---|
| Breakfast | | | | | | | | | |
| 2 | Meat | 5 | Eggs | 2 | | 14 | 10 | — | 146 |
| 1 | Bread | 4 | Bread | 1 sl | 25 | 2 | — | 15 | 68 |
| 1 | Milk | 1 | Skim milk | 1 c | 210 | 8 | — | 12 | 80 |
| 1 | Fruit | 1 | Grapefruit | ½ sm | 125 | — | — | 10 | 40 |
| 1 | Fat | 6 | Butter | 1 tsp | 5 | — | 5 | — | 45 |
| | | | | Total | | 21 | 15 | 37 | 379 |
| Lunch (or Supper) | | | | | | | | | |
| 2 | Meat | 2 | Cheese | 2 oz | 60 | 14 | 10 | — | 146 |
| 1 | Milk | 1 | Skim milk | 1 c | 240 | 8 | — | 12 | 80 |
| 1 | Vegetable | 2A | Asparagus and lettuce | ½ c | 100 | — | — | — | — |
| 1 | Bread | 4 | Bread | 1 sl | 25 | 2 | — | 15 | 68 |
| 1 | Fat | 6 | Mayonnaise | 1 tsp | 5 | — | 5 | — | 45 |
| 1 | Fruit | 3 | Peach | 1 med | 100 | — | — | 10 | 40 |
| | | | | Total | | 24 | 15 | 37 | 379 |
| Dinner (or Main Meal) | | | | | | | | | |
| 3 | Meat | 5 | Roast chicken | 3 oz | 90 | 21 | 15 | — | 219 |
| 1 | Vegetable | 2A | Cabbage | ½ c | 100 | — | — | — | — |
| 1 | Vegetable | 2B | Peas green | ½ c | 100 | 2 | — | 7 | 36 |
| 1 | Bread | 4 | Potato | 1 sm | 100 | 2 | — | 15 | 68 |
| 1 | Fat | 6 | Butter | 1 tsp | 5 | — | 5 | — | 45 |
| 1½ | Fruit | 3 | Plums | 3 med | 150 | — | — | 15 | 60 |
| | | | | Total | | 25 | 20 | 37 | 428 |
| Nourishment | | | | | | | | | |
| 1 | Milk | 1 | Skim milk | 1 c | 210 | 8 | — | 12 | 80 |
| ½ | Bread | 4 | Saltines | 2-3 | 10 | 1 | — | 8 | 36 |
| | | | | Total | | 9 | — | 20 | 116 |
| | | | | Day's Total | | 82 | 50 | 131 | 1302 |

For key to abbreviations see footnote p 122
Diet No III is employed to reduce the body weight of obese diabetic patients who barring acute complications are not receiving insulin

Diet No IV—1500 Calories
Protein 90 gm, Fat 47 gm Carb 180 gm
Division approx ⅓ for each meal with a bedtime nourishment

| No Exchanges | Food Exchange | List No | Sample Menu | Household Meas | Wt Gm | P | F | C | Cal. |
|---|---|---|---|---|---|---|---|---|---|
| Breakfast | | | | | | | | | |
| 2 | Meat | 5 | Eggs | 2 | | 14 | 10 | — | 146 |
| 2 | Bread | 4 | Bread | 1 sl | 25 | 2 | — | 15 | 68 |
| | | | Oatmeal | ½ c | 100 | 2 | — | 15 | 68 |
| 1 | Milk | 1 | Milk skim | 1 c | 240 | 8 | — | 12 | 80 |
| 1 | Fat | 6 | Butter | 1 tsp | 5 | — | 5 | — | 45 |
| 1 | Fruit | 3 | Grapefruit juice | ½ c | 100 | — | — | 10 | 40 |
| | | | | Total | | 26 | 15 | 52 | 447 |
| Lunch (or Supper) | | | | | | | | | |
| 2 | Meat | 5 | Frankfurter | 2 | 100 | 14 | 10 | — | 146 |
| 1 | Milk | 1 | Milk skim | 1 c | 240 | 8 | — | 12 | 80 |
| 1 | Vegetable | 2A | Sauerkraut | ½ c | 100 | — | — | — | — |
| 2 | Bread | 4 | Rolls | 2 sm | 70 | 4 | — | 30 | 136 |
| 1 | Fat | 6 | Butter | 1 tsp | 5 | — | 5 | — | 45 |
| 1 | Fruit | 3 | Applesauce | ½ c | 100 | — | — | 10 | 40 |
| | | | | Total | | 26 | 15 | 52 | 447 |
| Dinner (or Main Meal) | | | | | | | | | |
| 3 | Meat | 5 | Roast lamb | 3 oz | 90 | 21 | 15 | — | 219 |
| 1 | Vegetable | 2A | Chard | ½ c | 100 | — | — | — | — |
| 1 | Vegetable | 2B | Carrot strips | ½ c. | 100 | 2 | — | 7 | 36 |
| 2 | Bread | 4 | Potato | 1 sm | 100 | 2 | — | 15 | 68 |
| | | | Bread | 1 sl | 25 | 2 | — | 15 | 68 |
| 1½ | Fruit | 3 | Watermelon | 1½ c | 260 | — | — | 15 | 60 |
| | | | | Total | | 27 | 15 | 52 | 451 |
| Nourishment | | | | | | | | | |
| 1 | Milk | 1 | Milk, skim | 1 c | 240 | 8 | — | 12 | 80 |
| 1 | Bread | 4 | Graham crackers | 2 | 20 | 2 | — | 15 | 68 |
| | | | | Total | | 10 | — | 27 | 148 |
| | | | | Day's Total | | 89 | 45 | 183 | 1493 |

For key to abbreviations see footnote, p 122

Diet No IV is employed temporarily when a slow or slight reduction in weight is indicated Insulin therapy may or may not be used in con ion with this diet

DIET NO V—1700 CALORIES

*Protein 90 gm Fat 55 gm Carb 210 gm*

Division approx ⅓ of diet for each meal*

| NO EXCHANGES | FOOD EXCHANGE | LIST NO | SAMPLE MENU | HOUSEHOLD MEAS | WT GM | P | F | C | CAL |
|---|---|---|---|---|---|---|---|---|---|
| Breakfast | | | | | | | | | |
| 2 | Meat | 5 | Eggs | 2 | | 14 | 10 | — | 116 |
| 1 | Fat | 6 | *Butter* | 1 tsp | 5 | — | 5 | — | 45 |
| 2 | Fruit | 3 | Banana | 1 sm | 100 | — | — | 20 | 80 |
| 2½ | Bread | 4 | Bread | 1½ sl | 38 | 3 | — | 23 | 104 |
| | | | **Wheaties** | ¾ c | 20 | 2 | — | 15 | 68 |
| 1 | Milk | 1 | **Milk, skim** | 1 c | 240 | 8 | — | 12 | 80 |
| | | | | Total | | 27 | 15 | 70 | 523 |
| Lunch (or Supper) | | | | | | | | | |
| 3 | Meat | 5 | Egg | 1 | — | 7 | 5 | — | 73 |
| | | | Tuna | ½ c | 60 | 14 | 10 | — | 116 |
| 1 | Milk | 1 | Milk skim | 1 c | 240 | 8 | — | 12 | 80 |
| 1 | Vegetable | 2A | Lettuce | ¼ head | 100 | — | — | — | — |
| 1 | Vegetable | 2B | Pickled beets | ½ c | 100 | 2 | — | 7 | 36 |
| 2 | Bread | 4 | Bread | 2 sl | 50 | 4 | — | 30 | 136 |
| 1 | Fat | 6 | Butter | 1 tsp | 5 | — | 5 | — | 45 |
| 2 | Fruit | 3 | Tangerine | 2 lg | 200 | — | — | 20 | 80 |
| | | | | Total | | 35 | 20 | 69 | 596 |
| Dinner (or Main Meal) | | | | | | | | | |
| 2 | Meat | 5 | Mackerel | 2 oz | 60 | 14 | 10 | — | 146 |
| 1 | Vegetable | 2A | Spinach | ½ c | 100 | — | — | — | — |
| 1 | Vegetable | 2B | Onions | ½ c | 100 | 2 | — | 7 | 36 |
| 1 | Fat | 6 | Oil | 1 tsp | 5 | — | 5 | — | 45 |
| 2 | Fruit | 3 | Apricots | 4 med | 200 | — | — | 20 | 80 |
| 3 | Bread | 4 | Potato | 2 sm | 200 | 4 | — | 30 | 136 |
| | | | **Bread** | 1 sl. | 25 | 2 | — | 15 | 68 |
| 1 | Meat | 5 | **Egg** | 1 | — | 7 | 5 | — | 73 |
| | | | | Total | | 29 | 20 | 72 | 584 |
| | | | | Day's Total | | 91 | 55 | 211 | 1703 |

* Though this diet is divided into approximately three equal meals a milk and a bread exchange are indicated in bold type in the breakfast and in the dinner menus One or both of these designated nourishments can be deducted from the respective meal and given at other times of the day in keeping with the insulin therapy as outlined on pages 108 to 111 The same provision is made in the subsequent diets VI to XI

For key to abbreviations see footnote p 122

DIET NO VI—1900 CALORIES
Protein 90 gm Fat 69 gm Carb 230 gm
Division approx ⅓ of diet for each meal*

| NO EXCHANGES | FOOD EXCHANGE | LIST NO | SAMPLE MENU | HOUSEHOLD MEAS | WT GM | P | F | C | CAL |
|---|---|---|---|---|---|---|---|---|---|
| Breakfast | | | | | | | | | |
| 2 | Meat | 5 | Eggs | 2 | — | 14 | 10 | — | 116 |
| 2 | Fat | 6 | Butter | 2 tsp | 10 | — | 10 | — | 90 |
| 2 | Fruit | 3 | Orange juice | 1 c | 200 | — | — | 20 | 80 |
| 3 | Bread | 4 | Bread | 2 sl | 50 | 4 | — | 30 | 136 |
| | | | Bread | 1 sl | 25 | 2 | — | 15 | 68 |
| 1 | Milk | 1 | Milk, skim | 1 c | 240 | 8 | — | 12 | 80 |
| | | | | Total | | 28 | 20 | 77 | 600 |
| Lunch (or Supper) | | | | | | | | | |
| 2 | Meat | 5 | Oysters | 10 | 90 | 14 | 10 | — | 116 |
| 1 | Milk | 1 | Milk skim | 1 c | 240 | 8 | — | 12 | 80 |
| 1 | Vegetable | 2A | Mixed vegetable salad | ½ c | 100 | — | — | — | — |
| 3 | Bread | 4 | Oyster crackers | ½ c | 20 | 2 | — | 15 | 68 |
| | | 4 | Bread | 2 sl | 50 | 4 | — | 30 | 136 |
| 3 | Fat | 6 | Butter | 3 tsp | 15 | — | 15 | — | 135 |
| 2 | Fruit | 3 | Peach | 4 halves | 200 | — | — | 20 | 80 |
| | | | | Total | | 28 | 25 | 77 | 615 |
| Dinner (or Main Meal) | | | | | | | | | |
| 2 | Meat | 5 | Steak | 2 oz | 60 | 14 | 10 | — | 116 |
| 1 | Vegetable | 2A | Tomato sliced | 1 | 100 | — | — | — | — |
| 1 | Vegetable | 2B | Peas, green | ½ c. | 100 | 2 | — | 7 | 36 |
| 2 | Fat | 6 | Butter | 2 tsp | 10 | — | 10 | — | 90 |
| 1 | Fruit | 3 | Pear | 1 sm | 100 | — | — | 10 | 40 |
| 4 | Bread | — | Bread | 3 sl. | 75 | 6 | — | 45 | 204 |
| | | | Bread | 1 sl | 25 | 2 | — | 15 | 68 |
| 1 | Meat | 5 | Cheese | 1 oz | 30 | 7 | 5 | — | 73 |
| | | | | Total | | 31 | 25 | 77 | 637 |
| | | | | Day's Total | | 87 | 70 | 231 | 1902 |

* footnote p. 126
For key to abbreviations see footnote p 122

Diet No VII—2100 Calories
Protein 95 *gm*, Fat 75 *gm*, Carb 260 *gm*
Division approx ⅓ of diet for each meal*

| NO EXCHANGES | FOOD EXCHANGE | LIST NO | SAMPLE MENU | HOUSEHOLD MEAS | WT GM | P | F | C | CAL. |
|---|---|---|---|---|---|---|---|---|---|
| Breakfast | | | | | | | | | |
| 2 | Meat | 5 | Eggs | 2 | — | 14 | 10 | — | 146 |
| 1 | Fat | 6 | Butter | 1 tsp | 5 | — | 5 | — | 45 |
| 1½ | Fruit | 3 | Prunes | 3 med | 38 | — | — | 15 | 60 |
| 4 | Bread | 4 | Bread | 3 sl | 75 | 6 | — | 45 | 204 |
| | | | Bread | 1 sl. | 25 | 2 | — | 15 | 68 |
| 1 | Milk | 1 | Milk, whole | 1 c | 240 | 8 | 10 | 12 | 170 |
| | | | | Total | | 30 | 25 | 87 | 693 |
| Lunch (or Supper) | | | | | | | | | |
| 2 | Meat | 5 | Cold cuts | 2 sl | 90 | 14 | 10 | — | 146 |
| 1 | Milk | 1 | Milk, whole | 1 c | 240 | 8 | 10 | 12 | 170 |
| 1 | Vegetable | 2A | Lettuce and cucumber | ½ c | 100 | — | — | — | — |
| 1 | Vegetable | 2B | Carrots | ½ c | 100 | 2 | — | 7 | 36 |
| 3 | Bread | 4 | Bread | 3 sl | 75 | 6 | — | 45 | 204 |
| 1 | Fat | 6 | Butter | 1 tsp | 5 | — | 5 | — | 45 |
| 2 | Fruit | 3 | Grapes | 24 | 150 | — | — | 20 | 80 |
| | | | | Total | | 30 | 25 | 54 | 681 |
| Dinner (or Main Meal) | | | | | | | | | |
| 3 | Meat | 5 | Chicken | 3 oz | 90 | 21 | 15 | — | 219 |
| 1 | Vegetable | 2A | String beans, young | ½ c | 100 | — | — | — | — |
| 1 | Fat | 6 | Butter | 1 tsp | 5 | — | 5 | — | 45 |
| 1 | Vegetable | 2B | Winter squash | ½ c | 100 | 2 | — | 7 | 36 |
| 2 | Fruit | 3 | Pineapple | 1 c. | 160 | — | — | 20 | 80 |
| 4 | Bread | 4 | Biscuits | 3 | 105 | 6 | — | 45 | 204 |
| | | | Bread | 1 sl. | 25 | 2 | — | 15 | 68 |
| 1 | Meat | 5 | Egg | 1 | — | 7 | 5 | — | 73 |
| | | | | Total | | 38 | 25 | 87 | 725 |
| | | | | Day's Total | | 98 | 75 | 228 | 2099 |

* See footnote, p 126
For key to abbreviations see footnote p 122

Diet No VIII—2300 Calories
Protein 95 gm Fat 89 gm Carb 280 gm
Division approx ⅓ of diet for each meal*

| No Exchanges | Food Exchange | List No. | Sample Menu | Household Meas | Wt Gm | P | F | C | Cal |
|---|---|---|---|---|---|---|---|---|---|
| Breakfast | | | | | | | | | |
| 2 | Meat | 5 | Eggs | 2 | — | 14 | 10 | — | 146 |
| 2 | Fat | 6 | Butter | 2 tsp | 10 | — | 10 | — | 90 |
| 2 | Fruit | 3 | Orange sliced | 2 sm | 200 | — | — | 20 | 80 |
| 4 | Bread | 4 | Bread | 3 sl | 75 | 6 | — | 45 | 204 |
| | | | Ralston | ⅔ c | 100 | 2 | — | 15 | 68 |
| 1 | Milk | 1 | Milk, whole | 1 c | 210 | 8 | 10 | 12 | 170 |
| | | | | Total | | 30 | 30 | 92 | 758 |
| Lunch (or Supper) | | | | | | | | | |
| 2 | Meat | 5 | Crab meat | ½ c | 60 | 14 | 10 | — | 146 |
| 1 | Milk | 1 | Milk whole | 1 c | 210 | 8 | 10 | 12 | 170 |
| 1 | Vegetable | 2A | Tomato juice | ½ c | 100 | — | — | — | — |
| 1 | Vegetable | 2B | Peas green | ½ c | 100 | 2 | — | 7 | 36 |
| 4 | Bread | 3 | Bread | 4 sl | 100 | 8 | — | 60 | 272 |
| 1 | Fat | 6 | Butter | 2 tsp | 10 | — | 10 | — | 90 |
| 1½ | Fruit | 3 | Banana | ¾ sm | 75 | — | — | 15 | 60 |
| | | | | Total | | 32 | 30 | 94 | 774 |
| Dinner (or Main Meal) | | | | | | | | | |
| 2 | Meat | 5 | Lamb chops | 2 sm | 60 | 14 | 10 | — | 146 |
| 1 | Vegetable | 2A | Lettuce | ¼ head | 100 | — | — | — | — |
| 1 | Vegetable | 2B | Beets | ½ c | 100 | 2 | — | 7 | 36 |
| 3 | Fat | 6 | Butter | 2 tsp | 10 | — | 10 | — | 90 |
| | | | French dressing | 1 tbsp | 15 | — | 5 | — | 45 |
| 1 | Fruit | 3 | Cherries | 10 lg | 75 | — | — | 10 | 40 |
| 5 | Bread | 4 | Bread | 3 sl | 75 | 6 | — | 45 | 204 |
| | | | Lima beans | ½ c | 90 | 2 | — | 15 | 68 |
| | | | Soda crackers | 3 | 20 | 2 | — | 15 | 68 |
| 1 | Meat | 5 | Cheese | 1 oz. | 30 | 7 | 5 | — | 73 |
| | | | | Total | | 33 | 30 | 92 | 770 |
| | | | | Day's Total | | 95 | 90 | 278 | 2302 |

* footnote p 126
Key to abbreviations see footnote, p 122

Diet No IX—2500 Calories
Protein 100 gm Fat 100 gm Carb 300 gm
Division approx. 1/3 of diet for each meal*

| NO EXCHANGES | FOOD EXCHANGE | LIST NO | SAMPLE MENU | HOUSEHOLD MEAS | WT GM | P | F | C | CAL. |
|---|---|---|---|---|---|---|---|---|---|
| Breakfast | | | | | | | | | |
| 2 | Meat | 5 | Eggs | 2 | — | 14 | 10 | — | 146 |
| 3 | Fat | 6 | Butter | 3 tsp | 15 | — | 15 | — | 135 |
| 2 | Fruit | 3 | Orange juice | 1 c | 200 | — | — | 20 | 80 |
| | Bread | 4 | Bread | 3½ sl | 87 | 7 | — | 53 | 210 |
| | | | Maltex | ½ c | 100 | 2 | — | 15 | 68 |
| | Milk | 1 | Milk, whole | 1 c | 240 | 8 | 10 | 12 | 170 |
| | | | | Total | | 31 | 35 | 100 | 839 |
| upper) | | | | | | | | | |
| | Meat | 5 | Cold beef | 2 oz | 60 | 14 | 10 | — | 146 |
| | Milk | 1 | Milk, whole | 1 c. | 240 | 8 | 10 | 12 | 170 |
| 1 | Vegetable | 2A | Escarole raw | ½ c | 100 | — | — | — | — |
| 1 | Vegetable | 2B | Carrots | ½ c | 100 | 2 | — | 7 | 36 |
| 4 | Bread | 4 | Bread | 4 sl | 100 | 8 | — | 60 | 272 |
| | Fat | 6 | Butter | 3 tsp | 15 | — | 15 | — | 135 |
| | Fruit | 3 | Applesauce | 1 c. | 200 | — | — | 20 | 80 |
| | | | | Total | | 32 | 35 | 99 | 839 |
| in Mea ) | | | | | | | | | |
| | Meat | 5 | Roast pork | 2½ oz | 75 | 17 | 12 | — | 176 |
| | Vegetable | 2A | Cole slaw | ½ c | 100 | — | — | — | — |
| | Vegetable | 2B | Peas green | ½ c. | 100 | 2 | — | 7 | 36 |
| 4 | Bread | 4 | Biscuits | 2 | 70 | 4 | — | 30 | 136 |
| | | | Sweet potato | ½ c | 100 | 4 | — | 30 | 136 |
| 3 | Fat | 6 | Butter | 3 tsp | 15 | — | 15 | — | 135 |
| 2 | Fruit | 3 | Grapes | 24 | 150 | — | — | 20 | 80 |
| 1 | Meat | 5 | Cottage cheese | ¼ c | — | 7 | 5 | — | 73 |
| 1 | Bread | 4 | Saltines | 5 | 20 | 2 | — | 15 | 68 |
| | | | | Total | | 36 | 32 | 102 | 810 |
| | | | | Day's Total | | 99 | 102 | 301 | 2,318 |

* See footnote p 126
For key to abbreviations see footnote p 122

DIET NO X—2700 CALORIES
Protein 110 gm Fat 109 gm Carb 320 gm
Division approx ⅓ of diet for each meal*

| NO EXCHANGES | FOOD EXCHANGE | LIST NO | SAMPLE MENU | HOUSEHOLD MEAS | WT GM | P | F | C | CAL |
|---|---|---|---|---|---|---|---|---|---|
| Breakfast | | | | | | | | | |
| 2 | Meat | 5 | Eggs | 2 | — | 14 | 10 | — | 146 |
| 3 | Fat | 6 | Butter | 3 tsp | 15 | — | 15 | — | 135 |
| 2 | Fruit | 3 | Grapefruit | 1 sm | 250 | — | — | 20 | 80 |
| 5 | Bread | 4 | Bread | 4 sl | 100 | 8 | — | 60 | 272 |
| | | | Cheerio | ¾ c | 20 | 2 | — | 15 | 68 |
| 1 | Milk | 1 | Milk, whole | 1 c | 240 | 8 | 10 | 12 | 170 |
| | | | | Total | | 32 | 35 | 107 | 871 |
| Lunch (or Supper) | | | | | | | | | |
| 3 | Meat | 5 | Tuna | ¾ c | 90 | 21 | 15 | — | 219 |
| 1 | Milk | 1 | Milk whole | 1 c | 240 | 8 | 10 | 12 | 170 |
| 1 | Vegetable | 2A | Celery and lettuce | ½ c | 100 | — | — | — | — |
| 1 | Vegetable | 2B | Onions | ½ c | 100 | 2 | — | 7 | 36 |
| 4½ | Bread | 4 | Bread | 4 sl | 100 | 8 | — | 60 | 272 |
| | | | Saltines | 2 3 | 10 | 1 | — | 8 | 36 |
| 2 | Fat | 6 | Butter | 2 tsp | 10 | — | 10 | — | 90 |
| 2 | Fruit | 3 | Plums | 4 | 200 | — | — | 20 | 80 |
| | | | | Total | | 40 | 35 | 107 | 903 |
| Dinner (or Main Meal) | | | | | | | | | |
| 2 | Meat | 5 | Lamb chops | 2 sm | 60 | 14 | 10 | — | 146 |
| 1 | Vegetable | 2A | Lettuce and chives | ½ c | 100 | — | — | — | — |
| 1 | Vegetable | 2B | Rutabaga | ½ c | 100 | 2 | — | 7 | 36 |
| 5 | Fat | 6 | Butter | 5 tsp | 25 | — | 25 | — | 225 |
| 1 | Fruit | 3 | Pineapple | ½ c | 80 | — | — | 10 | 40 |
| 6 | Bread | 4 | Bread | 3 sl | 75 | 6 | — | 45 | 204 |
| | | | Potato, mashed | 1 c | 200 | 4 | — | 30 | 136 |
| | | | Graham crackers | 2 | 20 | 2 | — | 15 | 68 |
| 1 | Meat | 5 | Cottage cheese | ¼ c | 45 | 7 | 5 | — | 73 |
| | | | | Total | | 35 | 40 | 107 | 928 |
| | | | | Day's Total | | 107 | 110 | 321 | 2702 |

* See footnote p 126
For key to abbreviations see footnote [f] p 122

DIET NO XI—2900 CALORIES
Protein 120 gm Fat 120 gm Carb 335 gm
Division approx ⅓ of diet for each meal*

| NO EXCHANGES | FOOD EXCHANGE | LIST NO | SAMPLE MENU | HOUSEHOLD MEAS | WT GM | P | F | C | CAL |
|---|---|---|---|---|---|---|---|---|---|
| Breakfast | | | | | | | | | |
| 2 | Meat | 5 | Eggs | 2 | — | 14 | 10 | — | 116 |
| 3 | Fat | 6 | Butter | 3 tsp | 15 | — | 15 | — | 135 |
| 2 | Fruit | 3 | Prunes | 4 | 50 | — | — | 20 | 80 |
| 5 | Bread | 4 | Bread | 4 sl | 100 | 8 | — | 60 | 272 |
| | | | Rice Krispies | ¾ c | 20 | 2 | — | 15 | 68 |
| 1½ | Milk | 1 | Milk, whole | 1½ c | 360 | 12 | 15 | 18 | 255 |
| | | | | Total | | 36 | 40 | 113 | 956 |
| Lunch (or Supper) | | | | | | | | | |
| 3 | Meat | 5 | Cold cuts | 2 sl | 90 | 14 | 10 | — | 146 |
| | | | Cheese American | 1 sl | 30 | 7 | 5 | — | 73 |
| 1 | Milk | 1 | Milk whole | 1 c | 210 | 8 | 10 | 12 | 170 |
| 1 | Vegetable | 2A | Lettuce and cucumber | | 100 | — | — | — | — |
| 1 | Vegetable | 2B | Beets | ½ c | 100 | 2 | — | 7 | 36 |
| 5 | Bread | 4 | Bread | 5 sl | 125 | 10 | — | 75 | 340 |
| 3 | Fat | 6 | Butter | 3 tsp | 15 | — | 15 | — | 135 |
| 2 | Fruit | 3 | Banana | 1 sm | 100 | — | — | 20 | 80 |
| | | | | Total | | 41 | 40 | 114 | 980 |
| Dinner (or Main Meal) | | | | | | | | | |
| 3 | Meat | 5 | Liver | 3 oz | 75 | 21 | 15 | — | 219 |
| 1 | Vegetable | 2A | Tomatoes | ½ c | 100 | — | — | — | — |
| 1 | Vegetable | 2B | Onions | ½ c | 100 | 2 | — | 7 | 36 |
| 4 | Fat | 6 | Butter | 4 tsp | 20 | — | 20 | — | 180 |
| 1 | Fruit | 3 | Orange sliced | 1 | 100 | — | — | 10 | 40 |
| 6 | Bread | 4 | Noodles | ½ c | 100 | 2 | — | 15 | 68 |
| | | | Bread | 3 sl | 75 | 6 | — | 45 | 204 |
| | | | Sponge cake | 1½ cube | 25 | 2 | — | 15 | 68 |
| | | | Saltines | 5 | 20 | 2 | — | 15 | 68 |
| 1 | Meat | 5 | Cheese | 1 oz | 30 | 7 | 5 | — | 73 |
| | | | | Total | | 42 | 40 | 107 | 956 |
| | | | | Day's Total | | 119 | 120 | 334 | 2892 |

* See footnote p 126

For key to all deviations see footnote p 122

CHAPTER XIV

# Insulin Therapy

**Introduction.** *In the contemplation of insulin therapy the following considerations will apply*

(a) Salient features governing insulin need

(b) Is insulin therapy advisable and, if so,

(c) Which insulin preparation or combination of insulin therapies is indicated what is the correct timing of the administration of the insulin in relation to meals how is the proper dosage determined and under what circumstances is the insulin regimen changed?

(d) Administration of insulin

## A SALIENT FEATURES GOVERNING THE NEED FOR INSULIN

Familiarity with the various insulin preparations and the rate, degree and duration of their respective activities is necessary for the proper selection and the most effective combinations of insulins for the individual patient Individualization is the essence of insulin therapy No two patients

TABLE 19

ALTERATIONS IN DIET AND THE CHANGING NEED FOR INSULIN

| PROTEIN (GM) | FAT (GM) | CARBOHYDRATE (GM) | CALORIES | G E (GM) |
|---|---|---|---|---|
| 80 | 120 | 150 | 2000 | 208 |
| | | Diet changed to | | |
| 80 | 70 | 280 | 2000 | 333 |

Increases in the carbohydrate and the theoretical glucose equivalent of the diet, as illustrated cause only a minor increase in the need for insulin so long as the total calories are not increased (G E = glucose equivalent)

may require the same dose of insulin Unlike most drug therapies the individual's need for insulin is determined by several factors and it is only after the amount of insulin given is adjusted to conform with the individual's "need pattern" that the diabetes is controlled Too often one hears the loose remark that one unit will "look after" a certain number of grams of glucose The insulin need does not conform to any such exact equivalent

and the claim that it does indicates a failure to understand *the multitude* of influences which determine the amount of insulin a patient may need In order to emphasize some fundamental dietary factors which affect the insulin need clinically, *several illustrative studies are offered*

*First*, a diet of 80 gm protein, 120 gm fat and 150 gm carbohydrate, giving a total value of 2000 calories (theoretical glucose equivalent or G E = 58 per cent of protein + 100 *per cent of carbohydrate* + *10 per* cent of fat = 208 grams) may be allowed (see Table 19) Let us assume that with this diet 60 units of insulin are necessary to control the diabetes The dosage of *insulin having been established, an abrupt change in the diet* is made to 80 gm protein, 280 gm carbohydrate and 70 gm fat—2000 calories (G E = 333 gm) It will be observed that the glucose equivalent *has been increased from 208 to 333 gm but the total calories have* been kept constant by reducing the fat content of the diet If the insulin need fluctuated only with the amount of carbohydrate allowed in diet, an increase of 60 per cent—or a dosage of 96 units—would be needed to control the diabetes as efficiently as 60 units had done previously This is not what happens With the abrupt increase in the carbohydrate of the diet some glycosuria and hyperglycemia usually occur, *but*, these changes are *small and* are readily overcome by the addition of only a few units of insulin Why is this so? The reason is that the total calories were kept unchanged and the only reason why there was any increase in the insulin dosage at all is that carbohydrate has stronger glycosuric and hyperglycemic effects than the caloric equivalent of fat [1, 2]

TABLE 20

ALTERATIONS IN DIET AND THE CHANGING NEED FOR INSULIN

| PROTEIN (GM) | FAT (GM) | CARBOHYDRATE (GM) | CALORIES | G E (GM) |
|---|---|---|---|---|
| 80 | 120 | 150 | 2000 | 208 |
| | | Diet changed to | | |
| 80 | 120 | 280 | 2520 | 338 |

Increases in the carbohydrate and total calories as illustrated cause relatively great increases in the insulin need

A *second phenomenon* and one of equal clinical significance is illustrated Had the initial diet in Table 20 (P. 80 gm, F 120 gm, and C 150 gm—2000 calories) been changed by merely adding the 130 grams of [illegible] (520) provided by it to make the new [illegible] calories, the increase in [illegible] sary to control the diabetes when the carbohydrate increase was accompanied by a reduction in fat Combining these two phenomena it is observed that the *total calories profoundly affect the insulin dosage and the carbohydrate allowance of the*

*diet can be greatly increased with only minor changes in the insulin need resulting, provided the total calories are not increased also*

A *third phenomenon* and one of utmost importance, clinically can be illustrated if a diet of protein 80 gm, fat 120 gm, carbohydrate 150 gm —2000 calories (theoretical glucose equivalent 208 gm) is replaced by a diet with approximately the same theoretical glucose equivalent but with a reduced total calories e g, protein 80 gm fat 50 gm, carbohydrate 155 gm, 1400 calories (G E 207 gm) (See Table 21) If the dietary influence on insulin need were confined to carbohydrate no change *in the insulin need would ensue This is not what happens There is a remarkable* reduction in the insulin need The *initial* reduction is due to the reduced

TABLE 21

ALTERATIONS IN DIET AND THE CHANGING NEED FOR INSULIN

| PROTEIN (GM) | FAT (GM) | CARBOHYDRATE (GM) | CALORIES | G E (GM) |
|---|---|---|---|---|
| 80 | 120 | 150 | 2000 | 208 |
| | | Diet changed to | | |
| 80 | 50 | 155 | 1400 | 207 |

Reduction of the total calories by reducing the fat but without appreciably altering the glucose equivalent as illustrated causes a marked reduction in the need for insulin

calories With progressive loss of weight and reduction in the total metabolism, there is also a progressive reduction in the insulin need

The foregoing phenomena, reproducible at will indicate that

1 Carbohydrate has a greater insulin demand than the caloric equivalent of fat.

2 The insulin need is governed to a large extent by the total caloric value of the diet

3 The combination of a low calorie diet and a reduction in body weight by reducing the total tissue metabolism exerts a profound insulin sparing action

4 The combination of a diet sufficiently high in calories to add to the body weight exerts an increase in the need for insulin which is progressive until the diet is reduced or until the body weight becomes stabilized This effect on the insulin is by virtue of the large amount of food plus the increased total metabolism that accrues with a gain in body mass

5 Similarly complications affect total metabolism and in doing so affect the insulin requirement All influences which increase the total metabolism with but one exception—physical exercise—increase the need for insulin These are increased caloric intake obesity, infections, fevers toxemias, pregnancy and thyrotoxicosis Contrariwise, all influences which reduce the total metabolism with but one exception—the cessation of physi

cal exercise—reduce the need for insulin These are reduction in caloric intake, reduction in weight, correction of infections, fevers and toxemias termination of pregnancy and the control or cure of thyrotoxicosis

The protein content of the diet is not subject to the great fluctuation observed in the fat and carbohydrate contents and also its effect on the insulin requirement is feeble *in contrast to that of carbohydrate and total* calories

### B. IS INSULIN THERAPY ADVISABLE?

Insulin therapy is indicated *at once in all*

1 Diabetic children

2 Underweight adults who have glycosuria and hyperglycemia

3 Patients having acute complications, whether the underlying diabetes is mild or not, if there is glycosuria or hyperglycemia at any time in the twenty four hours

4 Cases of pregnancy complicating diabetes

5 Patients with a history of a sudden onset of symptoms of diabetes within the three months prior to the consultation This applies to the patient with apparently mild diabetes who will obviously do well without insulin eventually, as well as to the patient with an obviously severe diabetes

Insulin therapy is indicated in the treatment for diabetes when this disorder is not or obviously will not be, controlled satisfactorily by suitable dietetic measures and exercise and during acute complications for all diabetic patients, many of whom under usual circumstances may not need it Some authorities give insulin, in the initial days of treatment, to all diabetic patients In favor of this plan is the more rapid control of the diabetes and the training of the patient in the administration of insulin while he is under competent supervision It also emphasizes that many patients can discontinue insulin The majority of diabetic patients have a mild diabetes and ultimately do not need insulin This information has a good effect in neutralizing a general and erroneous belief that once one uses insulin he must always use it Unfortunately this is usually true for the thin patient having severe diabetes, but it is not true for obese patients who have mild diabetes

All patients who have an acute onset of the diabetes, *which may be mild* or severe, should be given insulin with the hope that some may be cured These rare individuals are the young or the thin patients with severe diabetes who are ordinarily given insulin from the outset of treatment The obese, untreated diabetic patient has a mild diabetes which develops insidiously when the body mass has increased to such an extent and has been maintained for a sufficient period to exhaust an already reduced pancreatic reserve

The amount of insulin needed is not relative to the degree of hyperglycemia with any constancy, nor can it be calculated with any degree of exactness according to the amount of sugar in the urine If glycosuria exists in the case of a patient taking insulin, more insulin is needed, but what 5 units will do in ridding the urine of sugar in one patient may require 25, or more, units in another

It is a good working rule, barring acute complications which will be considered later, that *all untreated diabetic patients who are considerably overweight will not need insulin* notwithstanding the presence of a high fasting blood sugar level on the first examination Every physician who sees many diabetic patients has seen fat patients with blood sugar levels above 300 mg per 100 cc and yet insulin was not necessary to control their diabetes

It is a good working rule, too, that *all children and underweight diabetic patients require insulin* even if the initial level for fasting blood sugar should not be high The certainty that insulin will be needed by growing children and underweight adults is based on the knowledge that to promote normal health and physical growth, a gain in weight and a liberal diet, each of which increase the need for insulin, are necessary The combination of a persistently elevated fasting blood sugar level and undernutrition makes insulin therapy imperative if good health is to be restored It has been our practice at the Pennsylvania Hospital never to give insulin to overweight diabetic patients unless during some acute complication and unless there has been a recent sudden onset of the diabetes The merit for the control of the diabetes should go to the dietetic measures and not to a preliminary and temporary course of insulin treatment In this manner the patient can be deeply impressed by the value of a restricted diet Approximately 40 per cent of the patients currently attending the metabolic clinic at the Pennsylvania Hospital do not need insulin We have observed the effect of insulin on obese diabetic patients at other clinics and, for the purposes of study, have given insulin to similar patients Knowing that the diabetes is inherently mild and that the reduction of a few pounds in weight would control it, one might expect that a small dose of insulin would suffice to accomplish the same result *This is not so* These patients are relatively resistant to insulin Repeatedly over 100 units of insulin a day were necessary to accomplish in reducing the blood sugar level what was as readily obtained by a slight reduction in weight These patients have three means to control their diabetes without insulin viz, a low caloric diet, a reduction in weight, and physical exercise All three are powerful agents in reducing the need for insulin Various attempts have been made, especially by Himsworth,[2] to classify diabetic patients into insulin resistant and insulin sensitive groups Most of the insulin resistant patients were middle aged or overweight There seems to be a general lack of appreciation for

the fact that the overweight insulin resistant patient loses this resistance to insulin in direct proportion to the reduction of body weight Any factor which reduces the total metabolism, with one exception (i e, the cessation of physical exercise), aids in the control of the diabetes Reduction in body mass seems to be the most effective of these factors Newburgh has confirmed our work and extended the proof of benefit secured by reduction in weight in the obese diabetic patient

*The effect of a reduction in weight* by virtue of a reduced caloric intake is illustrated in Table 22 One to several weeks are needed, as a rule, to control the diabetes in these overweight patients All who are familiar with the effect of obesity on life expectancy agree that overweight should

TABLE 22

Typical Response of the Blood Sugar Level and Glycosuria in the Obese Diabetic Patient to the Restriction of the Total Caloric Content of the Diet Without the Aid of Insulin

*A Fe Female White Aged 51 Height 61 Inches Ideal Weight 135 Lbs 39 Per Cent Overweight*

| DATE | WEIGHT LBS | DIET | | | GLYCOSURIA | BLOOD SUGAR MG PER 100 cc |
|---|---|---|---|---|---|---|
| | | P | C | CALORIES | | |
| July 7 1933 | 188 | 70 | 80 | 1100 | 2 1% | 250 |
| July 21 | 184 | 70 | 80 | 1100 | 0 | 177 |
| July 28 | 181½ | 70 | 80 | 1100 | 0 | 141 |
| August 11 | 179 | 70 | 80 | 1100 | 0 | 122 |
| October 20 | 170 | 70 | 95 | 1300 | 0 | 115 |
| January 26 1934 | 167¼ | 70 | 85 | 1200 | 0 | 110 |
| August 24 | 153 | 70 | 95 | 1300 | v ft trace | 113 |
| March 8 1935 | 148 | 70 | 105 | 1400 | 0 | 113 |
| July 12 | 147 | 70 | 115 | 1600 | 0 | 110 |
| October 9 1936 | 157½ | 70 | 115 | 1600 | 0 | 110 |
| December 10 | 156 | 70 | 140 | 1600 | 0 | 120 |
| June 25 1937 | 165 | 75 | 160 | 1800 | 0 | 113 |
| August 13 | 161 | 75 | 160 | 1800 | 0 | 109 |

*Summary* With a loss of weight of 9 pounds the blood sugar level fell from 0 250 per cent to normal Subsequently the carbohydrate tolerance was much improved Even with an increase in weight of 14 pounds from the lowest level the blood sugar remained normal

be corrected In the diabetic this result, accomplished by appropriate dietary measures, carries a double benefit—it cures the obesity and controls the diabetes

If, for any reason, the body weight is not reduced and the diabetes is not controlled, prolonged and needless hyperglycemia and glycosuria should not be allowed Insulin should be employed This is a recognition of failure, however The patient *will lose weight without insulin,* as he should if he is convinced of the advantages that will accrue, and if he has the will power to resist excess food Hospitalization, training and reassur

ance are essential to the successful treatment in most of these problem cases

The obese patient's appetite is greater and a reduction in weight is more difficult to secure if he is given insulin While insulin is harmless to such patients it misleads the patient into thinking that it is insulin, not the diet, that is important Besides it is a wasteful practice

## C WHICH INSULIN†

There are five insulins commercially available—regular (or unmodified), crystalline,* protamine zinc insulin, globin and the recently released NPH insulin which is another modified insulin

**Protamine Zinc Insulin.** This type of insulin is slowly absorbed and hence its blood-sugar lowering effect does not gain much headway in the first two or four hours after the injection (Fig 3) The slow absorption of this insulin provides its greatest advantage—a *prolonged effect* The blood sugar depressing effect of a dose of protamine zinc insulin lasts for twenty four to thirty six hours *In spite of the overlapping effect of the waning dose with that of the newly injected dose the combined effects are not adequate in most cases to prevent marked hyperglycemia and glycosuria during the forenoon*

*It is always well to give the protamine zinc insulin in one dose daily* one hour before breakfast unless combined with regular insulin

Its greatest effect will be exerted during the daytime six to eighteen hours after injection when three meals come in close succession, and its diminishing effect will be exerted after midnight It should be clear that the diminishing effect may in the absence of food during the long night period, be quite sufficient to provoke a hypoglycemia in the early morning This is the time that a *hypoglycemia due to protamine zinc insulin is most likely to occur The larger the dose the more delayed is the maximum effect and the more likely are hypoglycemic reactions to occur in the early morning A dose of 60 units of protamine zinc insulin* was observed, in the course of a special study to have its *greatest effect from twelve to twenty*

* Crystalline insulin (zinc insulin crystals in solution) has an effect indistinguishable from that of regular insulin The elimination of this insulin will reduce the confusion incident to the increasing number of insulins Eli Lilly & Co has stopped the commercial manufacturing of crystalline insulin

† NPH insulin (N neutral P protamine H Hagedorn) is a neutral crystalline protamine zinc insulin which acts more promptly in reducing the blood sugar than protamine zinc insulin—similar in this respect to globin insulin—and the blood-sugar lowering effect persists for at least twenty four hours.

The advantages claimed for NPH insulin are It is stable with little or no excess of protamine regular insulin can be added to NPH insulin without much loss of its rapid blood-sugar lowering action it fills the insulin need of a larger number of diabetic patients than is possible with protamine zinc insulin or globin insulin and the necessity of making insulin mixtures is somewhat reduced. There can be no doubt from our experience that this is a valuable insulin and when used in conjunction with suitable adjustments in diet and when necessary with added regular insulin it is superior to protamine zinc insulin for clinical practice

hours after its injection, even though 20 grams of carbohydrate were given at two hour intervals throughout the period of observation (Fig 3) In clinical practice, the diminishing effect during the night is highly desirable, *there being no food taken at this time* *Occasionally* we hear of a dose of protamine zinc insulin being given before supper This practice would mean that the greatest intensity of the insulin action would be in operation during the early hours before breakfast and at a time when it is preferable to have the blood sugar lowering effect on the wane

A small dose of protamine zinc insulin may suffice to control the diabetes in relatively mild cases In the more severe cases when larger amounts of insulin (especially if more than 20 units) are needed, two features stand out (a) The slowness of insulin action permits the diabetes to get out of hand' in the forenoon, and (b) there is an increased risk of hypoglycemic reactions in the early morning These two features are corrected *first*, by the addition of a dose of regular insulin in the morning which acts promptly and tends to prevent the hyperglycemia and glycosuria in the forenoon, *second*, by a reduction of the dose of protamine zinc insulin, and *third*, by giving a bedtime nourishment, as indicated in the standard diets, pages 126 to 132

Protamine zinc insulin permits fewer injections of insulin, reduces the *extent of oscillations of the blood sugar and controls the nocturnal blood* sugar level It has reduced complications, notably ketosis, and many patients, who formerly would have had to weigh their food, do well using household measurements, because of protamine zinc insulin

From the practical standpoint protamine zinc insulin suffices to control the diabetes without supplementary regular insulin, in a very small percentage of patients, although the percentage successfully treated with this insulin alone can be extended by reducing the carbohydrate for breakfast and giving a bedtime nourishment

To determine the dose of protamine zinc insulin we follow *three* simple rules

(a) Part of the breakfast carbohydrate is given at bedtime

(b) Daily, or on alternate days, the insulin is increased, from a safe *initial dose of approximately 12 units, by 4 to 12 units, depending on* the degree of glycosuria * *No further increases are made when the first urine* voided before breakfast becomes free from sugar

(c) At this point two specimens of venous blood are taken for sugar

* During hospitalization complete fractional urine collections are made over specified periods namely 7 to 11 A M 11 A M to 4 P M, 4 to 9 P M and 9 P M to 7 A M, and are examined for sugar At home suitable adjustments of the insulin dosage are made on the basis of tests made on single specimens of urine voided before each meal and at bedtime

*It is often desirable for patients who rarely have glycosuria to test only the specimen most likely to contain sugar* This information is presented in Table 23 according to the plan of insulin therapy employed.

TABLE 23

VARIOUS INSULINS IN THE TREATMENT OF DIABETES IN THE ABSENCE OF ACUTE COMPLICATIONS

| INSULIN | TIME ADMINISTERED | NUMBER OF DOSES PER DAY | GREATEST RISK OF HYPOGLYCEMIA (time) | SPECIAL NOURISHMENT (time) | BLOOD SUGAR TESTS — TIME OF | URINE: SPECIMEN MOST LIKELY TO CONTAIN SUGAR | URINE: SPECIMEN MOST LIKELY TO BE FREE FROM SUGAR |
|---|---|---|---|---|---|---|---|
| P Z I (alone) | 1 hour before breakfast | one | 2 A.M. to breakfast | bedtime | fasting and 3 P.M. | before lunch and at bedtime | before breakfast |
| Globin (alone) | 1 hour before breakfast | one | 3 P.M. to supper | 3 to 4 P.M. | fasting and 3 P.M. | before breakfast and before lunch | before supper and at bedtime |
| P Z I and Globin (injected separately) | 1 hour before breakfast | one of each | P Z I<br>2 A.M. to breakfast<br>Globin<br>3 P.M. to supper | 3 to 4 P.M. and bedtime | fasting and 3 P.M. | before lunch | before supper and before breakfast |
| P Z I and Regular (separately or mixed) | 15 minutes before breakfast<br>If 2 doses of regular, the 2nd dose is given before supper | (a) one of each<br>(b) one of P Z I and 2 of regular<br>(c) one of a mixture | P Z I<br>2 A.M. to breakfast<br>Regular<br>before lunch, or after a dose before supper, in late evening | bedtime and 11 A.M. (if desired) | fasting and 3 P.M. | bedtime | before breakfast and before lunch |
| NPH | 1 hour before breakfast | one | 4 P.M. to midnight | 3–4 P.M. and bedtime | fasting, 11 A.M. and 3 P.M. | before lunch | before supper and bedtime |
| NPH and Regular (mixed 4:1) | 15 minutes before breakfast | one | before lunch and 4 P.M. to midnight | 3–4 P.M. and bedtime | fasting and 3 P.M. | before breakfast | before lunch, before supper and at bedtime |

*Relative considerations concerning time of administration of insulin, the number of doses per day,* the time that hypoglycemic reactions are most likely, special nourishment and the time of day at which a knowledge of the blood sugar value is most helpful (see p. 142), the specimen of urine most likely to contain sugar and those most likely to be free from sugar are presented as they pertain to the various insulins. Special test days in which a blood sugar value is determined before each meal and at bedtime are frequently employed.

determinations, one before breakfast and one two hours after lunch If the fasting blood sugar value is below 120 mg per 100 cc, *it is not safe, because of the danger of early morning hypoglycemic reactions, to increase the protamine zinc insulin*, and if the post cibum blood sugar is below 160 mg per 100 cc and there is no sugar in the urine voided before each meal, we conclude that the diabetes is adequately controlled In anticipation of a reduction in the need for *insulin moderate reductions in dosage*

TABLE 24

SATISFACTORY (A) AND UNSATISFACTORY (B) CONTROL OF THE DIABETES WITH ONE DOSE OF PROTAMINE ZINC INSULIN DAILY

PATIENT A

Tests for Glycosuria

| Day of Treatment | Insulin PZI (Units) | 9 PM–7 AM | 7 11 AM | 11 AM–4 PM | 4 9 PM | Blood Sugar (mg per 100 cc) |
|---|---|---|---|---|---|---|
| 4 | None | ++ | ++++ | +++ | +++ | |
| 5 | 8 | ++ | +++ | ++ | ++ | |
| 6 | 8 | + | ++ | ++ | ++ | |
| 7 | 14 | + | ++ | ++ | + | |
| 8 | 14 | 0 | + | 0 | + | |
| 9 | 20 | 0 | + | 0 | 0 | |
| 10 | 20 | 0 | 0 | 0 | 0 | Fasting 80<br>Post-cibum 130 |

PATIENT B

| | | | | | | |
|---|---|---|---|---|---|---|
| 6 | 40 | 0 | ++++ | +++ | +++ | Fasting 66<br>3 PM 250 |

Indications for patient B One dose of globin insulin (see Table 25A) or a combination of protamine zinc and regular insulins (see Table 26)

are advisable after a few days of freedom from glycosuria *It will be noted* in Tables 24 to 28, with the exception of the initial blood sugar determination, the degree of glycosuria is used as a guide to therapy until the urine becomes free from sugar, at which time pre and post cibum blood sugar determinations are done on the same [illegible]

*Fasting blood sugar values alone* [illegible] *ading* In fact, it is a simple matter to [illegible] fasting [illegible] normal with protamine zinc insulin al[illegible] s not en[illegible] m blood sugar values should not be [illegible] Fasti[illegible] determinations have

their place but, unfortunately, it is rather universal that they are the only blood sugar analyses done

Usually, if the insulin need exceeds 20 units, *one* dose of protamine zinc insulin will not suffice for adequate control of the diabetes In such cases the fasting blood sugar value may be below 120 mg and yet the two-hour post cibum value exceeds 200 mg as illustrated in Table 24 B, with glycosuria *before* lunch, supper and at bedtime These are indications for an insulin which exerts a more prompt effect in the daytime and a shorter duration of action than occurs with protamine zinc insulin Globin insulin

TABLE 25

GLOBIN INSULIN THERAPY SATISFACTORY (B) UNSATISFACTORY (C)

PATIENT B

Tests for Glycosuria

| Day of Treatment | Insulin (units) | 9 P.M.–7 A.M. | 7–11 A.M. | 11 A.M.–4 P.M. | 4–9 P.M. | Blood Sugar (mg per 100 cc) |
|---|---|---|---|---|---|---|
| 6 | 40 (P.Z.I. 1 hr a.c.) | 0 | ++++ | +++ | +++ | Fasting 66<br>3 P.M. 250 |
| 7 | 40 (Globin 1 hr a.c.) | 0 | ++ | 0 | + | |
| 8 | 44 | 0 | + | 0 | 0 | Fasting 124<br>3 P.M. 96 |
| PATIENT C | | | | | | |
| 12 | 80 Globin | ++ | ++++ | 0 | 0 | Fasting 210<br>3 P.M. 80<br>(Hypoglycemia at 4.30 P.M.) |

Indications for Patient C One dose each of protamine zinc insulin and regular insulin given 15 minutes before breakfast (Table 26A)

fulfills these criteria and is the insulin of choice for those patients with diabetes of the next grade of greater severity (see Table 25) Or, a modest reduction of the protamine zinc insulin with a small dose of regular insulin injected separately, or, the same total amount given as a 2 1 mixture of regular and protamine zinc insulin, respectively, may be the next step

**Globin Insulin.** A single dose of globin insulin given daily one hour before breakfast will control a considerably *higher* percentage of the cases of diabetes than is possible to do with a single daily dose of protamine zinc insulin In fact, experience has shown that one dose of globin insulin daily can completely replace the single-dose therapy of protamine zinc in-

sulin and successfully extend its sphere of usefulness to the control of diabetes of a more severe grade

The speed with which globin insulin reduces the blood sugar increases as the dosage is increased This effect is much more prominent than is the case with protamine zinc insulin (Fig 3)

For the patient for whom one dose of protamine zinc insulin is not adequate, as indicated above, globin insulin may suffice and by this means

TABLE 26

PROTAMINE ZINC INSULIN AND REGULAR INSULIN THERAPY (INJECTED SEPARATELY) SATISFACTORY (C) UNSATISFACTORY (D)

PATIENT C

Tests for Glycosuria

| Day of Treatment | Insulin | 9 P M 7 A M | 7-11 A M | 11 A M - 4 P M | 4 9 P M | Blood Sugar (mg per 100 cc) |
|---|---|---|---|---|---|---|
| 12 | 80 Globin | ++ | ++++ | 0 | 0 | Fasting 210<br>3 P M 80 |
| 13 | 70 P Z I<br>12 Regular | ++ | + | + | + | |
| 14 | 70 P Z I<br>12 Regular | 0 | 0 | + | + | Fasting 118<br>3 P M 145 |

A 2 1 mixture of the regular and protamine zinc insulins frequently gives satisfactory results e g

| | | | | | | |
|---|---|---|---|---|---|---|
| 15 | 27 P Z I<br>54 Regular | 0 | 0 | + | 0 | |

PATIENT D

| | | | | | | |
|---|---|---|---|---|---|---|
| 8 | 80 P Z I<br>24 Regular | 0 | 0 | ++++ | ++++ | Fasting 80<br>3 P M 275 |

Indications for Patient D One dose each of protamine zinc and globin insulin given 1 hour before breakfast (see Table 28D)

multiple doses or a mixture of insulin may be avoided To determine the dosage of globin insulin the following rules (see Table 25) are recommended

(a) Ordinarily, only one dose of globin insulin is given daily and this is administered approximately one hour before breakfast (Globin insulin is not given before supper, except in rare cases and then in small amounts If this timing of administration is employed it is important to realize that the most intensive insulin action from a pre supper dose occurs during the night )

(b) A portion, usually one milk and one carbohydrate exchange, is taken from the breakfast and is given to the patient between 3 and 4 P M daily as a means of reducing the likelihood of a hypoglycemia before supper when the apparent effect of globin insulin is greatest Additions of 4 or 6 units on alternate days to the initial dose of 8 to 16 units are made until the specimen of urine voided before supper is free from sugar At this point 3 P M and fasting venous blood sugar values are determined If the patient is free from hypoglycemic reactions, if the 3 P M blood sugar is between 80 and 130 mg per cc, and if the fasting blood sugar does not exceed 130 mg per 100 cc the diabetes is under satisfactory control Moderate reductions in the dose of insulin are advisable after a few days of good control of the diabetes and a further decrease is usual when normal activities are resumed Further minor adjustments are made as indications arise The steps taken in arriving at the dosage of globin insulin as well as the detection of the cases in which it is not satisfactory are illustrated in Table 26 Some patients prefer globin insulin solely because there is practically no danger of a hypoglycemia during the night as exists with protamine zinc insulin We have delineated the sphere in which globin insulin is most valuable In this sphere it has in our experience yielded better results than other preparations or mixtures of insulin Globin insulin is almost universally satisfactory for patients not requiring more than 40 units daily and when the proper adjustment of the diet is observed In a decreasing percentage satisfactory results are secured with doses in excess of 40 units However one of our patients takes a single dose of 86 units of globin insulin with good results Like the other insulins globin insulin has its realm of best activity and we suspect that it is because the criteria used in arriving at the proper dosage are different from those for the other insulins that failures have resulted Globin insulin has a secure place in the treatment for diabetes until a better insulin than is available at present is discovered

If the 3 P M blood sugar value referred to above is between 80 and 130 mg per 100 cc and the fasting blood sugar is in excess of 200 mg with early morning glycosuria and glycosuria before lunch it is clear that further increases in the dose of globin insulin should not be made, because of the danger of hypoglycemia in the late afternoon, and yet, the diabetes is not well controlled Ordinarily we abandon globin in preference to a combination of regular and protamine zinc insulins under these circumstances

**Insulin Combinations** *Protamine Zinc Globin and Regular Insulin and Mixtures* An injection each of protamine zinc insulin and regular insulin is given one-half hour before breakfast when the rapid action of regular insulin and the prolonged action of protamine zinc insulin are needed The initial doses will vary but for purpose of illustration, 20 units of protamine zinc insulin and 6 units of regular insulin are injected

separately The urine voided before each meal and at bedtime is tested for sugar Daily increases of 2, or 4, or 6 units may be added to the regular insulin until the specimen before lunch becomes free from sugar Similarly, *the protamine zinc insulin is increased until the first specimen voided in the morning is free from sugar* At this point samples of blood for sugar determination are taken before each meal and at 9 P M This four test curve secured when circumstances warrant is of much greater value than single daily tests If all values are satisfactory—between 80 and 150 mg

TABLE 27

*Protamine Zinc and Globin Insulin Therapy (Injected Separately)* Satisfactory (D) Unsatisfactory (E)

PATIENT D

*Tests for Glycosuria*

| Day of Treatment | Insulin | 9 P M – 7 A M | 7 11 A M | 11 A M – 4 P M | 4 9 P M | Blood Sugar (mg per 100 cc) |
|---|---|---|---|---|---|---|
| 8 | 80 P Z I<br>24 Regular | 0 | 0 | ++++ | ++++ | Fasting 80<br>3 P M 275 |
| 9 | 70 P Z I<br>34 Globin | 0 | +++ | 0 | + | |
| 10 | 70 P Z I<br>34 Globin | 0 | ++ | 0 | + | Fasting 130<br>3 P M 100 |

To avoid 2 injections a mixture of regular and P Z I insulins may be tried 2 1—the results meet our standards in only 10 to 20 per cent of cases

PATIENT E

| | | | | | | |
|---|---|---|---|---|---|---|
| 8 | 80 P Z I<br>32 Globin | 0 | ++++ | 0 | +++ | Fasting 84<br>11 A M 280<br>3 P M 60<br>9 P M 230 |

Indications for Patient E A dose each of protamine zinc and regular insulin injected separately 15 minutes to ½ hour before breakfast and a small dose of regular insulin before supper (see Table 28)

per 100 cc—no further change is made, as in the case illustration in Table 26C In the more severe cases at 9 P M hyperglycemia may remain as the only unsatisfactory blood sugar value and there is also a 4 plus reaction for glycosuria on testing the 9 P M specimen Several methods are available to cope with this circumstance *First*, combined globin and protamine zinc insulin therapy (injected separately), illustrated in Table 27D, will correct the evening hyperglycemia and if given one hour before breakfast, a forenoon hyperglycemia may be prevented *When successful only two injections are needed* When this combination is used a milk and a

carbohydrate exchange is taken from the breakfast and given between 3 and 4 P.M. to insure against a hypoglycemia before supper due to globin insulin, and a milk and a carbohydrate exchange, deducted from the evening meal, are taken at bedtime, as illustrated in Figure 19, to guard against the risk of a hypoglycemia in the early morning hours due to protamine

TABLE 28

PROTAMINE ZINC AND REGULAR INSULIN BEFORE BREAKFAST AND REGULAR INSULIN BEFORE SUPPER TO CONTROL A SEVERE DIABETES

PATIENT F

Tests for Glycosuria

| Day of Treatment | Insulin | 9 P.M. 7 A.M. | 7 11 A.M. | 11 A.M. 4 P.M. | 4–9 P.M. | Blood Sugar (mg per 100 cc) |
|---|---|---|---|---|---|---|
| 8 | 80 P Z I<br>32 Globin | 0 | ++++ | 0 | +++ | Fasting 84<br>11 A.M. 280<br>3 P.M. 60<br>9 P.M. 230 |
| 9 | 80 P Z I<br>12 Regular before breakfast<br>10 Regular before supper | 0 | ++ | +++ | 0 | |
| 10 | 74 P Z I<br>18 Regular before breakfast<br>10 Regular before supper | 0 | 0 | ++ | 0 | Fasting 124<br>11 A.M. 140<br>3 P.M. 169<br>9 P.M. 110 |

One or the other of two alternative plans might be tried to avoid the three injections

(a) A mixture of regular and protamine zinc insulin 2 1 (occasionally 3 1)—initial dose being 68 units of regular and 34 units of protamine zinc insulin mixed and injected simultaneously from the one syringe

or

(b) A mixture (1 1) of NPH and regular insulins the initial dose being 80 units of NPH and 20 units of regular insulin

zinc insulin These adjustments in diet are not found to be inconvenient Patients like them They increase the patient's safety and they permit larger amounts of insulin to be given and better control of the diabetes results

In a *second*, or alternative plan, the protamine zinc insulin and regular

insulin given before breakfast are supplemented by a small dose of regular insulin before supper and adjusted until results are satisfactory (see Table 28) Injections of combined regular and protamine zinc insulin are properly given about fifteen minutes before breakfast If given longer before the meal the likelihood of hypoglycemic reactions is greater before breakfast, owing to the rapid action of regular insulin at the time in the twenty four hours when the blood sugar is usually lowest because of the retarded action of the protamine zinc insulin Because of the rapid action of regular insulin the full quota of food, one third of the total diet, after deducting a milk and bread exchange, is given for breakfast The one milk and one bread exchange are given at bedtime as a safety measure against a hypoglycemia in the early morning (Fig 17) The patient may take a portion of his lunch at 11 A M to increase the margin of safety against a hypoglycemia before lunch time Usually this measure is not necessary *Third* the total number of units found to control the diabetes by the two injections before breakfast and one before supper are given in a single injection as a 2 1 mixture* of regular and protamine zinc insulin or, rarely, a 3 1 mixture is more effective To guard against hypoglycemic reactions the same measures are taken as when two injections are given before breakfast and one before supper, presented above

Insulin mixtures are, at times, surprisingly satisfactory in controlling severe grades of diabetes This is the exception, however Not more than 20 per cent of our patients do as well as we want them to on the mixture therapy However, we believe that to avoid multiple doses the mixture method should be tried and if good results are not obtained separate injections are recommended

**Regular Insulin** There is an occasional patient who, because of allergic manifestations, is unable to use protamine zinc insulin In this event globin insulin, to which allergic responses are rarely, if ever, seen, may be tried In the event that neither of these insulins is tolerated recourse may be had to the use of regular insulin as it was employed in the pre-Hagedorn era

Examination of the fractional collections of urine for sugar already indicated is used as a guide in increasing the insulin until the urine is free from or contains only a trace of sugar

*One dose*, 8 to 12 units, of regular insulin given twenty minutes before breakfast may suffice to control a relatively mild diabetes Usually more is necessary While sugar continues to appear in the 7 to 11 A M specimens

* Protamine zinc insulin contains sufficient excess protamine to combine with added regular insulin up to approximately a 1 1 mixture [3] Hence if a rapid effect is expected from regular insulin added to protamine zinc insulin the ratio must be greater than 1 1 A ratio of 2 1 is the most widely effective mixture but a ratio of 3 of regular to 1 of protamine zinc insulin is used occasionally The results from mixtures of globin and regular insulin are in our experience, too unpredictable for clinical practice

2 to 6 units may be added daily When the dose reaches 18 or 20 units or if the 7 to 11 A M urine becomes free from sugar while the other fractions contain sugar, it is well to give *two doses* These may be given as follows 12 units twenty minutes before breakfast and 6 units before supper It is well to make no increase in the total dose at the time it is divided The mere splitting of the dose has the same effect as an increase The smaller the dose of regular insulin the more effective is each unit

Further increases, 2 to 4 units daily are made to the morning dose while glycosuria persists in the 7 to 11 A M urine fraction, and to the evening dose while there is sugar in the 4 to 9 P M fraction

*Three doses* are usually indicated when the amounts have reached the neighborhood of 20-0-16 The division might be as follows 16 units before breakfast 8 units before lunch and 12 units before supper, prescribed as 16-8-12 Small additions, 2 to 4 units, may be made daily as outlined above Glycosuria in the 11 A M to 4 P M collection indicates an increase in the noon dose while freedom from glycosuria would suggest no change This applies also to the other doses and specimens An occasional patient does better with a small third dose given at bedtime instead of before lunch

The foregoing plan of treatment serves the majority of these patients who require insulin There is, however, a group of more severe cases in which a point is reached when, if additions are made to any one of the three doses of insulin, a hypoglycemia results during the day and yet a hyperglycemia occurs in the early morning This is due to three large doses fairly close together on one hand and a long night period without insulin on the other The diabetes is so severe that when the effect of the evening insulin is exhausted and the patient has not enough endogenous insulin to keep the blood sugar at a normal level during the remainder of the night, a progressive increase in the blood sugar concentration occurs This accounts for the morning hyperglycemia despite the normal blood sugar values throughout the remainder of the day Allen[4] suggested lengthening the day periods between doses and shortening the night period without insulin by giving the morning insulin one hour earlier The timing of the noon dose remains unchanged but the evening dose is given one or two hours after supper When the severity of the diabetes calls for this plan, there need be no fear of a hypoglycemia during the night A portion of the supper may be taken at bedtime if a safeguard seems necessary

When a fourth dose is necessary, as occasionally occurs in patients having severe diabetes it is well to give it at midnight, with a small amount of nourishment (1 milk and 1 bread exchange) The other three doses, in event of the fourth dose being needed should be given prior to the respective meals The fourth dose is usually needed for a short period only

The great fields of usefulness for *regular insulin* are (1) in combination with protamine zinc insulin and with NPH insulin therapies, and (2) in the treatment during acute complications of diabetes (Chapter XVI)

## D ADMINISTRATION OF INSULIN

There is no feature in the treatment of diabetes that necessitates more detailed instruction than that of insulin administration In order that no important aspects be missed the instruction is dealt with under the following captions

1 Commercial brands of insulin
2 Preservation of insulin
3 Syringe and needle
4 Sterilization of equipment
5 Site of injection
6 Withdrawal of insulin
7 Technic of mixing insulins
8 Timing of injection

**1 Commercial Brands of Insulin.** There are four different insulins in widespread use

*Regular insulin* *
Globin insulin
Protamine zinc insulin
NPH insulin

Each insulin is available commercially in two strengths

U 40 red label 40 units per cc
U 80 green label 80 units per cc

Patients are trained to avoid confusion and error in measuring insulin by *always* using a syringe showing graduations up to 40 units per cc when U 40 insulin is being used and a syringe showing graduations to 80 units per cc in the case of U 80 insulin Serious errors of dosage—sometimes a double dose and other times one half a dose—are traceable to confusion resulting from measuring U 40 insulin on U 80 calibrations or vice versa Although accurate measuring is possible by this method it fosters confusion, errors and inaccurate recordings

Patients are taught that a unit of U 40 insulin has exactly the same effect as a unit of U 80 and that the reason for two different concentrations is that they allow, for patients taking large doses of insulin, the injection of twice as many units, by taking U 80 insulin instead of U 40, without increasing the volume of fluid injected

**2 Preservation of Insulin** Commercial insulins are remarkably stable *A bottle of insulin being drawn from daily does not need to be refrigerated* It does not deteriorate at room temperature even if the daily withdrawals are small Also, the injection of insulin at room temperature causes less discomfort and, in some cases less local reaction, and *greatly reduces, or possibly eliminates, the likelihood of subcutaneous fat* atrophy with disfiguring pitting of the skin We have had patients live in the tropics and use insulin at current atmospheric temperatures with no *bad effect Refrigeration is desirable for reserve supplies* of insulin and bottles from which some insulin has been withdrawn but which are not in

* Zinc insulin crystals in solution—crystalline insulin—is available but as its action is for practical purposes identical with that of regular insulin[5] and as its production has been greatly curtailed it is needless to deal with this insulin separately

daily use Freezing of insulin should be provided against, as it reduces its potency.

3 **Syringe and Needle.** The official insulin syringes* adopted by the American Diabetes Association[6] are available in three models

1 A 1 cc syringe with calibrations *for U 40 insulin* with markings in red enamel—total capacity 40 units
2 A 1 cc syringe with calibrations *for U 80 insulin* with markings in green enamel—total capacity 80 units, and
3 A 2 cc syringe calibrated for U 80 insulin with markings in green enamel total capacity 160 units

The markings in red and green enamel conform with the colors of the labels on the bottles of U 40 and U 80 insulins, respectively Confusion and mishaps will be reduced if these standard syringes are used exclusively for the administration of insulin

Needles ½ inch in length with 25 gauge and made of rustless steel, are to be preferred They are less likely to be broken and when the needle is thrust through the skin at right angles there is less risk of injecting the insulin intramuscularly than if longer needles are used If longer needles are preferred, injection at an angle of 45 degrees is advisable

4 **Sterilization of Equipment.** Alcohol sterilization of syringe and needle suffices provided they are not used to give injections to any but the one patient Alcohol does not destroy certain viruses, notably the hepatitis virus Outbreaks of hepatitis have occurred in diabetic clinics[7, 8] in which the sterilization of syringes was inadequate Alcohol sterilization of syringe and needle has been employed in some clinics in which the morning dose of insulin is administered by the nurse to the patient after the withdrawal of a sample of blood for testing If needles and syringes are to be used for more than one individual, sterilization should be by autoclaving, or by boiling for a minimum of *fifteen* minutes

The patient's personal equipment for insulin injection is organized on a tray or in a suitable container It comprises *Insulin, one bottle of alcohol —ordinary commercial rubbing alcohol is satisfactory—cotton, insulin syringe, and two needles* A stone—an Arkansas oil stone—upon which to sharpen needles is a useful adjunct

5 **Site of Injection.** Insulin is administered *subcutaneously—not* intramuscularly or intravenously (except as noted on p 231) When the patient makes the injection himself which is practically always the case except in very small children and during complications, the thighs and abdomen are the most convenient sites Some can also use the arms—over the deltoid muscles Subcutaneous injections by nurses are usually made into the deltoid and buttock regions The site should be varied in a manner that will prevent an injection in the same spot more than once in two

* These syringes may be secured locally or from Becton Dickinson Company Rutherford N J

weeks Injections should not be made into indurated areas or in close proximity to depressions due to decrease in subcutaneous fat

6 **Withdrawal of Insulin** A small ball of cotton is soaked with alcohol and used to thoroughly cleanse the rubber cap on the insulin bottle The pledget of cotton is then allowed to rest on top of the insulin bottle until the syringe and needle are prepared The needle is adjusted on the syringe and, with the full length of the needle immersed in alcohol, the plunger is withdrawn until the syringe is full of alcohol The alcohol is expelled into the bottle and air is drawn in and expelled repeatedly from the syringe *until the needle and syringe are dry*

Regular and globin insulins do not need to be agitated but protamine zinc insulin which tends to settle in the bottom of the bottle is uniformly suspended by rolling the bottle between one's hands It should not be shaken, as this causes bubble formation and interferes with making a homogenous distribution of the insulin which is contained in the milky particles

The next motion is to insert the needle through the cork into the insulin bottle and expel an amount of air, equal to or in excess of the dose of insulin to be withdrawn, into the bottle The insulin bottle is held in the inverted and vertical position and insulin is allowed to flow into the syringe This occurs without pulling on the plunger if the proper degree of positive pressure exists in the bottle A bubble or two may enter the syringe These are expelled into the bottle and the exact amount of insulin needed is measured and the needle is withdrawn from the bottle

The site for injection, having been selected, is thoroughly rubbed with the alcohol soaked pledget and the needle (1½ inch) is plunged full length and vertically through the skin After slight traction on the plunger reveals that the needle is not in a blood vessel the contents are discharged The needle is withdrawn and the area rubbed again with the alcohol soaked pledget If blood enters the syringe the needle is withdrawn half its length before discharging the insulin

The syringe is rinsed free of insulin by drawing alcohol into and discharging from the syringe several times *The bottle of alcohol should be* stoppered at all times except when in use Alcohol evaporates readily when exposed to the air, leaving water with no antiseptic properties

7 **Technic of Mixing Insulins.** The technic is modified when a mixture of insulins is used *Both insulin bottletops are cleansed with the bottles* standing upright and an amount of air equivalent to or in excess of the dose of the respective insulin to be withdrawn is injected into each bottle The air is injected *into the bottle of protamine zinc insulin first*—but no insulin is withdrawn—and then into the bottle containing regular insulin which is then inverted and the appropriate amount of insulin withdrawn *Regular insulin is always withdrawn first*—a measure which prevents the introduction of even minute quantities of protamine zinc insulin into the bottle of regular insulin The syringe is held in the vertical position with

the needle pointing upward The bottle of regular insulin is removed and the bottle of protamine zinc insulin is then substituted from which is drawn the proper amount of insulin

By holding the syringe upright throughout this maneuver the two insulins will, for practical purposes, remain unmixed in the syringe and if some bubbles must be returned to the protamine zinc insulin bottle this can be done without discharging any of the underlying regular insulin into the bottle containing the protamine zinc insulin Also, by maintaining positive pressure in each bottle, as directed, it will not be necessary to cope with the difficulty presented by a multitude of small bubbles in the syringe brought about when insulin is withdrawn against a negative pressure—the bubbles entering along the barrel of the syringe when the plunger is forcibly withdrawn With the proper amounts of each insulin in the syringe, the bottle of protamine zinc insulin is removed from the needle and the syringe is inverted several times in order to mix the insulins, which are then injected

8 **Timing of the Injection of Insulin.*** The time relationship between the injection of insulin and the taking of food depends largely on the type of insulin used (see Table 23) When protamine zinc only, or globin only, or a dose each of protamine zinc and globin insulin is used, the injection is given one hour before breakfast A mixture of regular and protamine zinc is injected about fifteen minutes, or immediately, before breakfast Regular insulin when employed to the exclusion of the slower acting insulins in the treatment for acute complications is injected just before meals (see p 215) The timing of the injection of regular insulin in the rare case of intolerance to the slowly acting insulins and in the absence of complications depends on the severity of the diabetes as to whether it is injected fifteen minutes before the taking of food or one hour before breakfast, just before lunch and one hour after supper or at bedtime This aspect is dealt with on page 148 Many injections of regular insulin, as given in the treatment for diabetic coma in the initial stages, have no relation to food or glucose administration (see p 231)

### COMPLICATIONS OF INSULIN THERAPY

(Hypoglycemia Allergic reaction Fat dystrophy Insulin edema Presbyopia Social problems )

*Hypoglycemia (Insulin Reaction)*†

**Causes and Nature of Hypoglycemic Reactions in Diabetes.** A hypoglycemic reaction occurs when too much insulin has been given in

* A single dose of NPH insulin is administered one hour before breakfast but if regular insulin has been added to NPH insulin the mixture is injected fifteen minutes or just before breakfast daily

† "Hypoglycemic reactions" or "insulin reactions" are the acceptable terms and are preferable to "insulin shock" which is misleading It is not until the patient is in extremis that it can truly be said that he is in shock *The signs and symptoms of a hypoglycemic reaction as usually observed are [illegible]ose of shock*

relation to food intake, physical exercise, decreasing resistance to insulin as complications subside, and to improving carbohydrate tolerance in the absence of complications The usual amount of insulin may prove to be excessive (a) if only a part of a meal is eaten, (b) if with the diet and *insulin constant there* is an unusual increase in physical exercise, (c) if appropriate reductions are not made in the insulin dosage as an acute infection subsides, (d) when the carbohydrate tolerance improves with the control of the diabetes, (e) if there is faulty distribution of the diet, or (f) if there is improper timing of the administration of insulin These are common causes of hypoglycemic reactions associated with insulin therapy but all features which tend to reduce the need for insulin predispose to hypoglycemic reactions The less common are included in Table 29

TABLE 29

CAUSES—FUNDAMENTAL AND PREDISPOSING—OF HYPOGLYCEMIAS DUE TO INSULIN THERAPY

A Fundamental
1 Too much insulin
2 Too little food

B Predisposing
1 Increased exercise
2 Faulty distribution of diet and vomiting
3 Improper timing of insulin injections
4 Improved tolerance as
a Diabetes is controlled
b Complicating ketosis infection or toxemia subsides
c Body weight is reduced
d Pregnancy is terminated
5 Undernutrition
6 Change in the site of insulin injection from an insulin tumefaction to other areas
7 Correction of thyrotoxicosis

An insulin reaction is characterized by a depression of the venous blood sugar level below normal—usually below 60 mg per 100 cc Values down to zero have been recorded

The onset of symptoms characteristic of a hypoglycemia commences at a higher blood sugar level when the hypoglycemia is due to regular insulin than when it is caused by protamine zinc insulin The slowness of the action of the latter, presumably, permits better adjustment to the falling blood sugar concentration, *hence when symptoms do occur they indicate a greater* depletion of the blood sugar than is the case when the reduction is brought about more rapidly As a result it is not uncommon to find venous blood sugar values as low as 55 or 60 mg per 100 cc, or even lower, without symptoms in the case of an overdose of protamine zinc insulin Ordinarily, this is not the case if these values are due to regular insulin

*Physical Exertion* Physical exertion in all but severe and untreated diabetes, has a blood sugar lowering effect This feature assumes special

importance in the patients taking large doses of insulin An adjusted sedentary regimen interrupted by a game of golf, tennis, hiking or other strenuous exercise is very likely to be complicated by a hypoglycemic reaction unless more food than usual has been ingested or unless a moderate reduction in the previous dose of insulin has been made The insulin need tends to be less, for many patients, in the summer time when increased exercise is the rule

*Faulty Distribution of the Diet* The failure to have the patient using globin insulin take a 3 to 4 P M nourishment predisposes to hypoglycemic reactions before supper The omission of bedtime nourishment by the patient taking protamine zinc insulin increases the likelihood of an insulin reaction before breakfast (see Table 23) Delayed or reduced meals are predisposing causes of insulin reactions If the patient is taking regular insulin before breakfast a reduced breakfast and a delayed lunch would operate in favor of an insulin reaction as would a reduced luncheon and delayed supper in the case of globin insulin therapy, and a reduced supper and omission or reduction of the bedtime nourishment in the case of protamine zinc insulin therapy Vomiting of food after insulin has been given leaves the patient exposed to a possible insulin reaction if the diabetes is controlled and if precautionary measures are not taken Small liquid feedings may be permitted at one-hour intervals until glycosuria is noted or if oral feeding is contraindicated glucose a 5 per cent solution in distilled water, may be administered slowly by vein

*Improper Timing of Insulin Injection* Patients taking both protamine zinc insulin and regular insulin before breakfast are more liable to have an insulin reaction if the insulin is given too long before breakfast Injection immediately before or not more than fifteen minutes before breakfast reduces this risk to a minimum We never give two daily doses of protamine zinc insulin, but if one dose is given before breakfast and a second is given before supper the danger of an early morning hypoglycemia is intensified In some instances we give a small dose of globin insulin before supper in addition to the larger maintaining dose before breakfast This practice, unless rigidly controlled predisposes to insulin reactions in the early morning

Overdosage of insulin, through error in measurement is an uncommon cause of hypoglycemia When it does occur it is usually associated with one of the following (a) insulin administered by some one not fully trained in the technic, (b) measuring insulin of one strength (U 80) in a syringe graduated for another (U 40), (c) errors in making mixtures of insulin, e g an erroneous reversal of a 2 1 mixture of regular and protamine zinc insulins would intensify the protamine zinc insulin action and predispose to a hypoglycemia in the early morning

*Improved Tolerance for Carbohydrate* The initial control of the diabetes with insulin is followed by a reduced insulin need in most cases This

improvement may be measured in terms of a few to many units Failing to anticipate this improvement by reducing the insulin, as control of the hyperglycemia is achieved, makes insulin reactions probable This gain in tolerance is noted in uncomplicated diabetes but it is much more marked when complications, notably infections, ketosis and toxemias, are brought under control The reduced insulin need may be measured in hundreds of units, and when suitable reductions are made insulin reactions are unlikely

*Undernutrition* Patients who receive insulin and at the same time are on a weight reducing regimen may develop insulin reactions as their weight decreases Reduction of body weight has a profound influence in reducing the need for insulin This is true of a reduction as a planned therapy but it also occurs in cases of malnutrition accompanying debilitating diseases such as malignant disorders and occasionally with the emaciation that occurs with tuberculosis

The *termination of pregnancy* in most cases is accompanied by an increased sensitivity to insulin As in the correction of obesity, the termination of pregnancy reduces the total metabolism and predisposition to hypoglycemic reactions is increased as a result

*Changing Site of Insulin Injection* Insulin may be relatively ineffective when injected into indurated areas or into insulin tumefactions but hypoglycemic reactions may be precipitated without changing the dose but by injecting the insulin into loose subcutaneous tissues

**Symptoms of Hypoglycemia** The symptoms characterizing varying degrees of severity of hypoglycemic reactions are as follows

*Mild Reaction* Mild hypoglycemic reactions exhibit symptoms of a stimulated sympathetic nervous system hunger, weakness, tremulousness nervous instability mild emotional disturbances, headache, mild mental confusion and depression, and a detached manner in answering questions

*Reaction of Moderate Severity* As the more severe grades of hypoglycemia develop disturbances in the central nervous system and psychiatric manifestations occur—increased weakness, excessive perspiration with skin cold and clammy to the touch, numbness of tongue, lips or buccal mucosa cardiac palpitation difficulty in mental concentration, loss of memory diplopia staring expression, blurring of vision, difficulty in walking, impaired coordination, increased emotional instability and disorientation

*Severe hypoglycemic reactions* include twitching of muscles, convulsions, unconsciousness, paraplegias, incontinence of urine and, in unusual cases, transient hemiplegia Protracted coma for hours or days even after the blood sugar is restored to normal may rarely occur Mental deterioration is a rare complication of prolonged severe hypoglycemic states Fatalities due to insulin reactions are rare. They are most likely to occur in debilitated individuals with poor glycogen ' least likely in the robust and muscular p ' ample s 1

Hypoglycemic ' e to , ulin may not be ob

served in the early stages They occur most frequently between m dn ght and breakfast t n e The j at ent may be found stuporous or in an uncon sc ous state drencl ed with per p rat on He may on the other hand feel weak on r s ng and l a e a cloud over l s m nd unt l he l as eaten Head ache is part cularly com non during an l follow ng the correct on of a hypo glycem a due to protam ne z nc nsul n Al o retrogra le amnes a is com mon I at ents may go about tl e r dut es in a dazed manner for ary ing per ods before attract ng attent on or before tak ng food and yet tl ey may l a e no recollect on of dr v ng home, of cros ng the street of the conclus on of an important meeting or other happen ngs ma y of wh ch carry the poss b l ty of gra e danger cl agr s r mpr sonn ent

*Illus at e Ca es* J H aged e gl y a s, I f her scl oo room and p oc eded to l home c os ng se al ma n thoroughfa es en rou e I was no un I her mo her n d l wolf ng her food ha an nsu n ea ion was su pected Upon ecovery I pa n ha l no recol ec on of l a ng lef he hool room o of fin l ng h way home Th s pa ent s now a college gradua e an l teach ng school

Pa ien E M an insurance salesman had no re ol ec on of wha occurred n a two hour period du ng wh h he drove h s au omob le unaccompan ed fo 18 miles along a bu y h ghway a ound traffic les o end by runn ng n o a post. He was found n a nea by field by sta e t oopers who on find ng h s d abe ic dent fication a d l d h n orange ju ce a supply of w h l ey found n he pa en s au omob le The poss b l es a end ng tl s ad en ure a e many Th s expe en e was the result of an a empt on the part of a carele pa ient o balance a break in d e restr ions w h an o er lose of nsul n.

**Diagnosis** A l story nd cat ng that the pat ent has d abetes an l s rece v ng i ul n treatment is helpful Th s nformat on is not always ob ta nable and even if it is the po b l ty of unconsc ousness result ng from other causes makes a careful different al d agnos s n portant

The pat ent in an nsul n react on n ay exh bit s g s rang ng from sl ght tra s tory moments of confus on to con plete unco s ou ess Tl e mode and t n e of onset of symj toms are important. Tl e pat ent may appear "queer a f xed express on is common and conversat on may be w thout *proper sequence He may bel ave l ke an auto aton He appears confused* and is emot onally upset over trivial matters or without apparent cause He n ay become bo sterous and re t exam nat on an l treatment Tl e on set of unconsciousne s before meal t me sl ould n ake one su pect l ypo glycem a wl le if t occurs between one and three l ours after a hearty n eal l ypoglycem a is less l kely to be tl e cau e

There is usually some pallor of tl e sk n but n general the pat ent s appearance is not tl at of a person who has been ll but that of one who has fainte l Tl e sk n is wet *Beads of per pirat on are common on the* f rel ead at tl e ha r marg n tl e face body an l extrem t es are col l a l clam my and tl e underclotl es are wet w th persp rat on The body tem perature may be sl ghtly below normal Tl e pup l are l lated tl e intra ocular tens on is not d turbed tl e pul e rate is ad anced w th normal or ncreased force and the blood pressure is e ther normal or as frequently

occurs, is elevated It falls below normal only when the patient is *in extremis* The breathing is undisturbed Marks from the injection of insulin are usually apparent on legs, arms or abdomen The tendon reflexes are overactive and a Babinski sign may be elicited during but not immediately after recovery from the reaction

The examination of the urine offers little of value in confirming the diagnosis The absence of glycosuria is suggestive evidence, however, in the case of an unconscious patient known to have diabetes and known to take insulin Furthermore the absence of glycosuria and ketonuria is definite evidence against diabetic ketosis On the other hand, the patient whose blood sugar goes quickly from a high to a low level may have sugar in the bladder urine from a preceding hyperglycemic phase Sugar in the first specimen obtained from the unconscious patient should not rule out the possibility of a hypoglycemia After the bladder has been emptied, a second specimen should contain no sugar in case of a hypoglycemia

A low blood sugar level, below 60 mg per 100 cc, is the most important single evidence *of an insulin reaction One must make a diagnosis on clinical* evidence however, and begin treatment The patient's welfare should not be jeopardized by delaying therapy until the blood sugar concentration is known

**Differential Diagnosis** The most frequent causes of unconsciousness likely to be confused with insulin reactions are alcoholism, diabetic coma (ketosis) and intracranial lesions Trauma, poisonings, epilepsy, uremia syphilis of the central nervous system, and rarely, hyperinsulinism, malaria and Addison s disease may simulate, in part, a hypoglycemia due to an overdose of insulin Night sweats of tuberculous infections complicating diabetes are occasionally suggestive of, and may be confused with an insulin reaction

*Diabetic Coma (Ketosis)* The chief characteristics of diabetic coma are presented on page 226 and the characteristic clinical differences between diabetic coma and an insulin reaction are presented in Table 30 In contrast to the patient having an insulin reaction, the patient in coma (ketosis) has received too little insulin, there is marked *dehydration and air hunger* (Kussmaul breathing) with an *odor of acetone on the breath*, the onset of symptoms is slow, at least eight to twelve hours, and is preceded by *anorexia, thirst, polyuria* and later *vomiting*, the *pulse* is weak and rapid and the blood pressure is subnormal, the *tendon reflexes* are diminished and the plantar reflexes are normal, there is usually no twitching of the muscles or convulsions, glycosuria and acetonuria are present, there is often a *complicating infection in the ketotic patient* and finally the blood sugar level is above normal, the plasma acetone is promptly detectable (see p 227) and the carbon dioxide combining power of the blood plasma is reduced

If there is any doubt whether one is dealing with diabetic coma (ketosis)

or an insulin reaction (hypoglycemia), the therapeutic test of giving glucose (dextrose), 20 cc of a 50 per cent solution in distilled water, intravenously, should be made. This will do the ketotic patient no harm and it will restore the hypoglycemic individual to consciousness in most cases.

*Intracranial Lesions.* The more common intracranial lesions that are likely to confuse one in making the diagnosis are: hemorrhage, thrombosis

TABLE 30

A Comparison of the Clinical Evidences of Hypoglycemia and Diabetic Coma (Ketosis)

| | HYPOGLYCEMIA | DIABETIC COMA (KETOSIS) |
|---|---|---|
| Cause | Too much insulin or not enough food | Not enough insulin |
| General appearance | A well person who has fainted | Very ill |
| Breathing | Normal | Rapid and deep (air hunger) |
| Onset | Rapid (minutes) | Slow, at least 12 hours |
| Hunger | Great | Anorexia |
| Thirst | None | Great |
| Vomiting | Rare | Common |
| Eyes | Staring and pupils dilated | Sunken |
| Disturbed vision | Diplopia and difficulty in focusing | Haziness |
| Headache | Common | Absent |
| Intraocular tension | Normal | Decreased |
| Skin | Wet (especially forehead) | Dry |
| Tissues | Normal | Dehydrated |
| Pulse | Full and rapid | Weak and rapid |
| Air hunger | Absent | Present |
| Blood pressure | Elevated or normal | Subnormal |
| Cardiac palpitation | Frequent | Absent |
| Constipation | None | Present |
| Muscular twitching | Common | Absent |
| Nervousness | Common | Absent |
| Babinski's sign | Common | Absent |
| Complicating infections | Absent | Common |
| Abdominal pain | Absent | Common |
| Urine sugar | None after residual urine is discarded | Present |
| Blood sugar | Below normal | Above normal |
| Acetonuria | Absent | Present |
| Response to treatment | Rapid (minutes) | Slow (hours) |

and emboli in cerebral vessels, tumors and trauma. A careful physical examination will reveal signs of arterial disease, localizing neurologic signs or evidence of trauma and there will be no marks of the insulin injection. The blood sugar level will be normal or moderately elevated and glycosuria is common when there is injury to the base of the brain. This response is due to stimulation of the sympathetic centers.

**Treatment of Hypoglycemia.** The hypoglycemia should be corrected without delay. Mild reactions are readily remedied by having the patient

drink a glassful (240 cc) of orange juice, or take four or six glucose lozenges (8 or 12 gm) All patients taking insulin should carry these lozenges or lumps of sugar with them Any sweets will serve the same purpose Cane sugar must be reduced to a monosaccharide before it is absorbed, hence is somewhat slower than glucose in correcting a hypoglycemia Honey, molasses, syrup and hard candy are all effective but if not available other carbohydrate foods may be given if the patient is able to take food by mouth Fruits, cereals, bread or crackers will correct mild reactions Often it is only necessary to take a meal a trifle earlier than usual and make suitable changes in the insulin dosage on the following day

There is danger in feeding an unconscious patient Atelectasis and pneumonia may result from the inhalation of food into the lungs during this procedure If there is no alternative the risk is reduced if the patient is held in a sitting position and fed slowly with a spoon Liquids should not be poured into the mouth of an unconscious patient One or two glucose lozenges or, lacking these, a lump of sugar placed between the cheeks and teeth will dissolve slowly and be swallowed with little risk

Dextrose 20 cc of a 50 per cent solution in distilled water is given intravenously without delay to the patient who is unconscious or having convulsions as a result of a hypoglycemia The recovery from unconsciousness is prompt Often consciousness is restored before the intravenous injection is completed Should this measure fail to restore consciousness a continuous intravenous administration of a 10 per cent solution of glucose (dextrose) in distilled water is begun This latter measure is rarely necessary but in instances in which enormous doses of insulin are taken by mistake it may be life saving Consciousness having been restored intravenous treatment is no longer necessary, but when the reaction is due to protamine zinc insulin it is a good plan to give 10 or 20 gm of carbohydrate half hourly or hourly until the next meal is taken or until glycosuria is provoked In this manner one can prevent hypoglycemic reactions due to protamine zinc insulin which are apt to recur because of the continued action of insulin after their temporary correction A recurrence of the reaction is not likely when the hypoglycemia follows overdosage with regular insulin

If sterile glucose is unobtainable and if feedings by mouth are not practical, carbohydrate in liquid form may be administered via a tube passed through one nasal passage and into the stomach The withdrawal of fluid which turns blue litmus red is proof that the tube is in the stomach and not in a bronchus This precautionary test should always be made Retention of food in the stomach may prevent absorption of carbohydrate hence too much reliance should not be placed on oral or tube feedings if there is not a prompt (within ten or fifteen minutes), satisfactory clinical response

The hypoglycemic individual absorbs considerable glucose if it is administered by rectum Twenty grams of glucose or corn syrup dissolved

in 6 ounces of warm water and given by the Murphy drip or intermittent methods have served well in emergencies on several occasions when instructions regarding treatment had to be given to the patient's relatives by long-distance communication

Epinephrine (adrenalin), 0 5 to 1 0 cc of a 1 in 1000 solution given subcutaneously, may cause a return of consciousness and allow food to be taken by mouth It operates by liberating glucose from glycogen Little effect can be expected from epinephrine in the emaciated patient or in the patient who has a severe reaction from protamine zinc insulin in which the hepatic glycogen is heavily drawn upon before symptoms of a hypoglycemia appear Epinephrine is effective in the well nourished patient and when the hypoglycemia is the result of an overdose of a rapidly acting insulin The effect of the epinephrine in any case is only transitory It should never be relied upon alone but should be supported by the administration of food

*Diabetic Identification Card* Every diabetic patient taking insulin should carry an appropriate identification card Such a card doubtless saved the lives of at least two of our patients and saved one patient from a sojourn in a prison cell The cards employed at the Pennsylvania Hospital carry the following information

I HAVE DIABETES AND TAKE INSULIN

If I am found ill unconscious or behaving unnaturally
Place a candy or lump of sugar between my cheeks and teeth or feed me orange juice slowly
If not improved in *15 minutes*
take or send me to a hospital or notify my physician

My name is

Address Telephone

My physician is

Address Telephone

**Prevention of Insulin Reactions (Hypoglycemia).** A recurrence of an insulin reaction may be prevented by reducing the insulin on the day following a reaction and on succeeding days If the reaction occurs before breakfast the protamine zinc insulin should be reduced by 2 to 8 units, if it occurs before lunch the morning dose of regular insulin is responsible and should be reduced by 2 to 8 units thereafter, if the reaction occurs in the late evening the dose of insulin given before supper should be reduced by a similar amount

It is not wise to reduce the insulin dosage without determining the cause of the reaction Should the hypoglycemia have followed unusual exercise,

an omitted meal or vomiting, no reduction is indicated on the following day if normal conditions are restored

Insulin reactions may be prevented in the following ways

1 A small reduction of the insulin dosage, of 4 to 12 units, is made when unusual and strenuous exercise is planned When the usual amount of insulin has been injected and extra exercise is taken a moderate addition to the usual diet, such as a banana, a glass of milk or a glass of orange juice, is advisable A regular daily plan of exercise, uniform in time and amount, will reduce the likelihood of reactions

2 In event of vomiting the amount of insulin is reduced to one-half the usual requirement if there is no glycosuria, keeping in mind that even if food is not ingested metabolism of the body tissues continues Rarely indeed should a dose be completely omitted, though this is a common (and dangerous) practice Each specimen of urine is examined separately and if heavy glycosuria should occur more insulin is given This plan is also adopted in case of diarrhea Close supervision of the diabetic patient who is vomiting or has diarrhea is essential, as in one patient they may cause hypoglycemic reactions and in another ketosis In case of vomiting, food by mouth should be stopped Nourishment in the form of a 10 per cent solution of glucose (dextrose) may be given by vein, one liter every eight hours At least one liter of normal saline is indicated in each twenty four hours, as are amino acid preparations, in protracted cases Regular insulin is given at six hour intervals (p 220) In case of diarrhea, bland foods and those which tend to cause constipation are allowed although intravenous therapy may be needed in severe cases

3 Appropriate reductions are made in the insulin dosage after the diabetes is brought under control A gain in carbohydrate and total food tolerance occurs at this time and the need for insulin decreases proportionately A decrease of 4 to 8 units a day until glycosuria occurs is a good practice At this point a small increase in the amount of insulin given will usually suffice to adequately control the diabetes Greater reductions should follow the reduction in body weight and eradication of ketosis, infections and toxemia

4 Increasing the insulin too rapidly is a cause of reactions which is easily avoided The increases in the amount of insulin given should be small—2 or 4 units daily—as control of the diabetes is approached

5 The timing and distribution of the insulin are arranged according to the plan presented on page 141 It is especially important, when a rapidly acting insulin and protamine zinc insulin are given before breakfast, that the meal be not delayed more than fifteen minutes after the insulins are administered The same is true of the evening meal if a dose of regular insulin is given before the meal This precaution is necessary because of the presence of a combined action of protamine zinc insulin and regular insulin at the end of a considerable period without food

6 The likelihood that reactions will occur before lunch is reduced, in the patient susceptible to reactions, by taking part of the lunch—the fruit or milk—at 10 30 or 11 A M Similarly the likelihood of early morning hypoglycemic reactions is greatly reduced by taking food at bedtime (see p 140). When globin insulin is employed, a milk and a bread exchange, deducted from the breakfast, and taken at 3 P M , aids in preventing late afternoon reactions

7. A small reduction—4 to 12 units—of the insulin dosage when the patient is discharged from the hospital is a wise precaution to offset the effect which the increased exercise has in precipitating low blood sugar levels

### *Allergic Reactions to Insulin*

Local reactions about the site of the insulin injection, believed to be allergic, are manifested by swelling redness, discomfort and itching They are common when protamine zinc insulin is used and unusual when the rapidly acting insulins or globin insulin are given Swollen and indurated areas about an inch or an inch and a half in diameter appear and become hot and tender These local reactions first appear from two to twelve hours after the injection is given The reaction is at its height from eighteen to twenty-four hours, after which the inflammatory reaction and the swelling gradually subside until there is no trace of them in three or four days In the sensitive patient, there may be three or four of these "areas" in the various stages of progression and regression at one time Fortunately within three or four weeks desensitization usually occurs spontaneously

It is rare to encounter a patient allergic to insulin protein itself identified by noting allergic reactions to all forms of insulin Allergic sensitivity to the specific animal protein is somewhat more frequent and is identified, as an example, when relief follows the change from insulin of pork origin to that made from beef * The most common of all allergic manifestations to insulin therapy are associated with sensitivity to protamine zinc insulin—alleviated spontaneously in most cases and in the persistent cases, by changing to globin insulin The addition of protamine —having no antigenic properties—to insulin a true antigen—is believed to create a higher incidence of sensitivity to insulin than when insulin alone is injected into individuals having no detectable sensitivity to protamine solution (Kern and Langner)[9] Resumption of insulin therapy after a lapse of weeks to years is followed in a week to ten days by systemic reactions urticaria swelling of face and extremities in some patients having an allergic sensitivity to insulin

By recrystallizing mixed beef and pork insulin several times Jorpes[10]

* Insulin available commercially is of pork and beef (mixed) origin with the exception of the Sharp & Dohme product which is of beef origin. Beef insulin is available on request from Eli Lilly & Company Recrystallized insulin is not commercially available in this country as yet

was successful in retaining the activity of the insulin while eliminating impurities which were considered to be the causes of the allergic reactions

It is rare to find a patient allergic to globin insulin but if sensitivity to the insulin protein is present—an uncommon occurrence—it is to be expected that allergic response will follow the injection of insulin of any brand or source

***Treatment for Allergic Reactions to Insulin.*** 1 *It* may be practicable to omit insulin This is always the case in the obese patient with uncomplicated diabetes Control of the diabetes by appropriate restriction in diet and reduction in weight will avoid untoward allergic reactions from insulin It must be assumed, however, that every diabetic patient will sooner or later develop acute complications and will need insulin temporarily It is therefore of great importance to clearly establish his allergic status and determine which insulin, if any, he can take without risk of severe allergic reactions If he has an allergic sensitivity to all insulins desensitization is recommended, after which insulin is given with sufficient frequency to avoid a return of his sensitivity In the case of the obese diabetic one injection per week will suffice, whereas daily injections will be needed for therapy in the thin diabetics

2 No special treatment is needed for the common local reactions which subside spontaneously after a few weeks of continued insulin therapy

3 Allergic reactions to protamine zinc insulin of sufficient severity to warrant more vigorous action usually subside by changing from protamine zinc insulin to globin insulin Changing of the commercial brand of insulin —from one lot of insulin to another or from the product of one pharmaceutical company to that of another—has been beneficial on some occasions This is attributable in most cases to changing the animal source of insulin

*Generalized urticaria or constitutional reactions, especially edema* of the face and mucous membranes dyspnea, prostration gastro intestinal symptoms and stiffness of joints following insulin administration are uncommon but present a genuine problem when they occur

These reactions as well as the persistence of severe local reactions are treated as follows

a Epinephrine hydrochloride (adrenalin) 1 1000, subcutaneously, 0 5 cc for an adult and 0 2 cc for a child The dose is repeated as frequently as every half hour depending upon the severity of the reaction In extreme emergencies epinephrine may be given intravenously but *at a very slow rate* and in doses of 0 3 to 0 5 cc

*b Ephedrine sulfate is given by mouth* 25 mg ($^3/_8$ gr ) for the adult and 8 mg (⅛ gr ) for the child, at four hour intervals until improvement occurs

c One of the antihistamine drugs is given orally at four hour intervals until relief is secured and maintained

Rapid desensitization is indicated when the reaction to each of the available insulins is severe in a person who must have insulin. The patient may have a severe infection or be in a state of pre-coma, or coma. In either case desensitization to allergic reactions to insulin may be life saving. We have given subcutaneous injections of minute quantities of regular insulin at ten- to twenty-minute intervals. Increases are made from the initial dose of 1/1000 of a unit to 1/500 to 1/250 and so on, doubling the dose for each successive injection until it reaches 1 unit. If no significant local reaction develops when this amount is given, therapeutic amounts are administered to control the diabetes. In this program of desensitization the anticipated increase is delayed and the same dose repeated in the event that an untoward local reaction develops. The desensitization to regular insulin is recommended because it is this brand of insulin that is used in the event of acute complications. It is important that no interruption in insulin therapy be permitted following desensitization, in this manner reducing to a minimum the return of hypersensitivity to insulin.

*Illustrative Case Report.* R. G., male, aged sixty-five years, with onset of diabetes *in October, 1939, took insulin from January until March, 1940. In August, 1940,* insulin was resumed because of a small carbuncle. After nine days the patient developed urticaria and his face began to swell, especially his lower lip and under his eyes. He was found, by intracutaneous tests, to be sensitive to all available (seven) brands of insulin. He was rapidly and successfully desensitized with regular insulin beginning with 1/500 of a unit in distilled water and doubling the dose at ten-minute intervals, except when a definite wheal formed, in which event no increase was made when the next injection was given. This program was continued until, within three hours, it was possible to give 1 unit subcutaneously. A dose of 5 units was then given subcutaneously without ill effect.

## *Fat Dystrophies*

**Insulin Tumefactions.** Local painless, indurated areas of fat hypertrophy sometimes occur where insulin is injected in the same area over long periods. The swelling is "rubbery" to palpation and the skin is adherent to the subcutaneous tissue. Not infrequently the overlying skin is peculiarly insensitive to pain. For this reason patients, especially children, wish to have the insulin injected into this area, but as the induration interferes with absorption of the insulin, this is a bad practice.

*Treatment* consists of changing the site of injection in such a manner that one site will not be used a second time in any fortnight. The swelling gradually subsides. Injections of insulin elsewhere with a more rapid absorption may precipitate hypoglycemic reactions unless suitable adjustments in the dosage are made.

**Fat Atrophy Due to Insulin.** Concave depressions in the cutaneous contour due to atrophy of subcutaneous fat and appearing in areas into which insulin has been injected over relatively long periods—several weeks to several years—are not uncommon in child diabetics of both sexes and of adult females—usually under thirty years of age (Fig. 20). The condi

tion is not common in the adult male diabetic population Fat atrophy in areas remote from the injected area has been reported

The cause of the fat atrophy at the site of the insulin injection is unknown beyond the fact that it is related to insulin therapy Many theories have been put forward in explanation of its cause—faulty technic of administration of insulin, impurities in the alcohol used for cleansing and sterilizing purposes, the preservative in insulin, local metabolic reactions the low temperature of insulin when injected, local injury and androgen insufficiency The sex and age occurrence suggests that the androgens may



*Fig 20 Fat Atrophy Concave pitting of the skin due to atrophy of fat in locations* used for injecting refrigerated insulin (Patient J H) This disfigurement disappeared in three months when insulin at room temperature was used and without changing the site of injection

have a protective effect against this disorder On the other hand, the paucity of subcutaneous fat in the adult male may be a factor The condition is not *restricted to insulin therapy, as repeated injections of pituitrin* in the treatment for diabetes insipidus are known to have caused it Varying of the sites of the injection has been recommended as a preventive measure In *our experience no local lipodystrophy has occurred* as long as the insulin injected is at room temperature In fact, this simple measure has led to the correction of the deformity without altering the site of injections

This disfiguring *but harmless condition is corrected* by varying the sites of injection of insulin in such a manner that a site will not be used for injection twice in any fortnight The injection of insulin which has been

allowed to reach room temperature is the most effective preventive measure The pitting disappears slowly, requiring from two to four months and rarely one to two years to subside completely

### *Insulin Edema*

A filling-out of the face, giving it a waxy appearance, smooth and free from wrinkling with a reduction of facial expression, is seen in some patients following the rapid control of a severe diabetes with insulin An imbalance in the osmotic pressure between circulatory and tissue fluids caused by withdrawal of glucose from the blood is believed to be responsible These patients are usually, but not always, young females One patient had not only the "insulin facies" but extensive edema of his extremities and disturbance of vision as well during the first few weeks he received insulin This patient had a complicating xanthoma diabeticorum with a blood cholesterol of 1666 mg per 100 cc and a severe diabetes The water retention probably was exaggerated by the high carbohydrate diet which was allowed

Ordinarily no special treatment is necessary for this "insulin edema though in the case referred to above the edema was so extensive that the salt was withdrawn from the patient's diet and for a few days he was given ammonium chloride, 1 3 gm (grains 20), three times daily It is well to investigate the kidney function of any diabetic who has demonstrable edema, which is one of the outstanding signs of an intercapillary glomerulonephritis (Kimmelstiel Wilson's disease) (see p 197)

### *Presbyopia Due to Insulin*

A transient presbyopia occurs in a considerable number of patients when they receive insulin for the first time This disturbance is attributed to a reduced elasticity of the lens and is probably the consequence of a disturbance of the adjusted osmotic pressure in the tissue of the lens and circulating fluids The result is difficulty in focusing vision on nearby objects The changes are bilateral The degree of change usually amounts to about 2 diopters but in the young patients, in whom the condition is most troublesome, changes of 8 diopters are sometimes observed This disturbing complication has occurred in my experience for the most part in young adult patients, whereas Wilder states "This disturbance in vision is much more marked in individuals who are approaching the age of natural presbyopia and whose lenses because of age, have already lost elasticity "

This disturbance is entirely apart from hypoglycemic reactions and fortunately after two to four weeks of treatment the presbyopia precipitated by insulin therapy, disappears entirely

The patient should be advised that the disturbance is temporary Glasses purchased at such a time, though satisfactory during the period of presbyopia, would gradually become unsuitable with the restoration of the

normal osmotic equilibrium between the lens and ocular fluids Examinations preparatory to prescribing for glasses should be delayed until at least six weeks have elapsed subsequent to control of the diabetes The temporary derangement will have disappeared by this time In isolated instances it may be desirable to overcome this disturbance in vision from the beginning of treatment by securing suitable lenses for temporary use

### *Insulin Therapy as a Social Problem*

All child diabetics need insulin and special consideration of their diets These factors tend to make them different from normal children Children resent "being different" more than do adults The adjustment problem is a great one It will require sympathetic understanding on the part of the doctor if the young patient's confidence is obtained to a degree which makes it more satisfying to the patient to heed his advice and derive the full benefits of treatment than it is to ' follow the crowd " This is a real test for the doctor It is a real test for the patient This feature is dealt with in more detail in Chapter XIX

Diabetic patients have a higher than average intellect, yet if it is known by a prospective employer that the candidate for a position has diabetes and uses insulin, the chances of employment are reduced if not eliminated The increasing number of diabetic patients intensifies this problem on a national and international scale

The diabetic who has a hypoglycemic reaction in public is suspected of being intoxicated If, by chance, he has the odor of alcohol on his breath during a hypoglycemic reaction, he may be subjected to the indignities attending arrest and to the danger of his unidentified hypoglycemia while awaiting a hearing One patient, because of his behavior in a restaurant where he sought relief from a hypoglycemic reaction, was considered to be drunk and was thrown out bodily The encounter with a police officer which followed, ended happily when the patient produced a diabetic identification card

Diabetic patients taking more than 20 units of insulin daily should not engage in occupations that expose them to power driven machinery or that entail the driving of an automobile The patient taking large amounts of insulin, who drives a private automobile, is cautioned that he should take extra food before doing so, especially if he does so just before meal time

The social problem which diabetes presents is a big one, and one of many varieties, concerning all ages, occupations and all walks of life In the treatment of diabetic patients a high degree of individualization is the rule The aims should be (a) to control the diabetes adequately without making the program so inflexible, or so exacting that to follow it can hardly be expected, (b) to adopt effective safeguards against hypoglycemic reactions—to maintain a high standard of health in general and to under

stand the individual's social problem and guide him in such a manner that in doing what gives him greatest satisfaction he will *include the measures* best suited to cope with his diabetes and his social adjustment

### *Insulin Resistance of Marked Degree*

Barring acute complications of diabetes severe degrees of idiopathic resistance to insulin are uncommon and their cause is unknown One of our patients (J G ) had an insulin need in 1947 which altered in a rhythmic fashion between 100 and 2800 units daily for many months The only apparent complicating factor was a cholelithiasis with no acute manifestations No abrupt change followed the cholecystectomy but over several months which followed, the need for insulin decreased gradually and when last seen in August, 1950, her diabetes was controlled by 176 units daily

Great increases in the resistance to insulin are common during (a) *acute complications*, notably infections, ketosis, acute disseminated pancreatitis, and uncommonly during acute parenchymal disease of the liver, and (b) *chronic complications*, especially the following allergic manifestations disease of the adrenal and pituitary glands and hemochromatosis

**Unknown Disorders.** It is the insulin resistance that elevates the daily need to extremely large doses—many hundreds of *units*—without any apparent cause that is the mystery These cases are rare in contrast to the common occurrence of insulin resistance, in excess of 200 units daily, occurring during acute complications

**Causes of Insulin Resistance.** When due to acute complications the insulin resistance rapidly subsides with control and correction of the precipitating condition, whereas insulin resistance due to undetectable causes tends to subside spontaneously but gradually over periods of months or years There is an occasional exception to this rule Smelo[11] reports a patient who required 700 to 800 units daily five and one half years after the onset of the insulin resistance Our patient (J G ) takes 176 units after three and one half years

In view of the fact that the underlying disturbance in the physiology of these chronic cases, without obvious complication, is entirely speculative a review of the subject here is not considered appropriate It suffices to place our suspicion on aberrations in the cellular enzyme system. Hormonal disturbances are known to increase the need for insulin but it is doubtful if this explains such cases as that referred to above, in which on careful evaluation no such disturbance was detected

It has been suggested that the insulin is excreted in the urine If so, it is not in an active form, as the injection into a mouse of appreciable quantities of such a patient's urine after a huge injection of insulin has no hypoglycemic effect

**Treatment of Insulin Resistance.** 1 Acute complications are d with as outlined in Chapter XVI

2 Insulin is given in sufficient amounts and with sufficient frequency to avoid ketosis When no cause is detected it may be necessary to treat these patients identically as one would treat them for an acute complication It was necessary, in the case of J G., to give *regular insulin in doses as high* as 475 units every four hours day and night over a prolonged period Attempts to give fewer doses or smaller amounts resulted in the prompt appearance of ketosis The ultimate favorable outcome, as illustrated by this case, is the rule

## INSTRUCTION OF THE PATIENT

Patients will benefit from a general knowledge of diabetes They will find a regular source of information written especially for them in *The Forecast,** a bimonthly publication Patients untutored in this subject are likely to abandon treatment and believe themselves cured All who treat diabetic patients have seen those who come for help because of failing vision, or peripheral vascular disease, or degenerative disease of the kidneys and who give a history of diabetes of which they believed themselves cured years previously We are not certain that diabetes is ever cured and in any case, if it is, the infrequency of this occurrence is such as to make it of no practicable importance except to that rare individual who is involved We hold out no hope of a cure from means now at hand but do try to dispel the fears that many patients have, fears born of a background of all the worst cases they have occasion to remember We owe it to these worried patients promptly to point out the comparison of the outlook for diabetic patients in the present with that of the pre insulin eras

A few days are spent in the hospital for the purpose of controlling the diabetes and instructing the patient However, this is but an introduction to a lifetime study and training The instruction deals with

1 General knowledge of diabetes
2 Causes of the symptoms of diabetes
   - Hunger
   - Thirst
   - Loss of weight
   - *Polyuria*
   - Weakness
3 Sugar in the urine
   - Source and amount
   - Relation to blood sugar
   - Tests for sugar in the urine
   - What urine specimens to test
   - Is sugar in the urine always an indication of diabetes?
4 The blood sugar
   - Normal values
   - Why blood sugar determinations are necessary
   - Range of blood sugar values in untreated diabetes and in controlled diabetes
5 Diet prescription
   - Protein fat carbohydrate and total calories

* Published by the American Diabetes Association Inc 11 West 42nd St New York 18 N Y

Diet menu from diet prescription
Selection and preparation of foods
Measuring of foods
Weighing of foods—rarely necessary
Distribution of diet

7 Exercise
Effect on patient's weight
Effect on blood sugar
Effect on need for insulin
Adjustment of diet and insulin needs because of exercise

8. Insulin
Need for insulin and dosage
Commercial brands and their identification
Administration
Sterilization and maintenance of equipment
Measurement and mixing when indicated
Site of injection
Timing of injection

9 Insulin reactions (Hypoglycemia)
Definition
Symptoms
Treatment
Cause and prevention
Times that reactions are most likely to occur

10 Changes in body weight and diabetes
Loss of weight in treatment for diabetes
Loss of weight in untreated diabetic patient
Gain in weight

11 What to do in case of unretained food—vomiting or diarrhea and in case of complete loss of appetite with aversion to food

12 Infections and diabetes
Sugar in urine
Blood sugar
Ketosis (coma)
What to do in case of infection

13 Diabetic coma (ketosis)
Definition
Causes
Prevention
What to do if ketosis is suspected

14 Care of the feet

15 Surgery and diabetes

16 Misbeliefs—especially about the outlook, insulin substitutes *there are none*—and insulin addiction

This training of the diabetic patient will carry over for weeks and months but before discharge from the hospital the patient should clearly understand

1 The preparation measuring or weighing in case this is necessary, and the distribution of the diet

2 The brand or brands of insulin he is receiving the dose he should take, the time of the injection and how and where to administer the insulin

3 The symptoms of an insulin reaction and how to correct them

4 How to test the urine for sugar and to know which specimen should be tested

5 How to keep an up to date record indicating dates, diet, insulin dosage and results of the tests for sugar in the urine

**Exercise.** Physical exercise, judiciously employed by patients who have no contraindicating *conditions, is of inestimable value in the treatment* for diabetes It improves the total food and carbohydrate tolerance and reduces the need for insulin In the overweight patient having a mild diabetes exercise has two beneficial effects, (a) an insulin like action in reducing the blood sugar level and (b) the reduction of body weight which reduces the need for insulin *Hence, the patient quickly learns* that glycosuria tends to occur when he is physically inactive and that it subsides when he is active

In untreated undernourished patients having severe diabetes exercise is not helpful but actually accentuates the wasting processes characteristic of this disease and the blood sugar level is increased instead of lowered But, exercise becomes a helpful instead of a harmful agent in these cases when the diabetes is adequately treated with diet and insulin Its blood sugar lowering effect is restored and all the advantages that accrue as the *result of a good physical condition are added The decrease in the need* for insulin following discharge from the hospital is largely due to the effect of exercise, an effect which is anticipated by a modest reduction in the insulin

Exercise as an instrument of therapy is best used by having the patient remain relatively active during the initial period of hospitalization—by making active exercise a daily routine and one of uniform extent and regularity *of time as far as practicability will permit An ordinary amount* of exercise *should never be curtailed* in the well treated diabetic unless some complication dictates otherwise Exercise producing undue fatigue is undesirable, however It will not always be possible to regulate the amount of exercise from day to day, hence the importance of teaching patients that increased exercise will have an effect similar to added insulin and that omission of exercise will have the opposite effect They are instructed that exercise during that time of day when they are most likely to have hypoglycemic reactions (see Table 23) will increase this risk Meals following increased exercise should not be delayed A reduction in the amount of insulin given prior to increased exercise is frequently advised Patients learn from experience what reduction serves best to prevent an insulin reaction on one hand or glycosuria on the other *The dose that is to be* reduced will depend upon the time of day that the extra exercise is taken *For instance, the patient* who takes protamine zinc insulin and regular insulin before breakfast and who elects to play tennis before lunch reduces the *regular insulin* by 6 to 12 units and does not delay his luncheon If on the other hand he or she spends the evening roller skating or dancing the reduction should be from the *protamine zinc insulin* and the bedtime nourishment might be increased but *under no circumstances omitted* The pa

tient taking a dose each of protamine zinc insulin and globin insulin before breakfast and who plans to undertake extra exercise during the afternoon may safely reduce the *globin insulin*, the amount being judged by experience according to the amount of exercise. Extra food at lunch and/or an increased 3 P.M. nourishment would reduce the need for a smaller dose of insulin.

In the case of a severe diabetes requiring a dose of regular insulin before supper, as well as regular and protamine zinc insulins before breakfast, the reduction is from the dose of insulin taken before supper in the event of extra exercise in the evening.

Adjustments counteracting the hypoglycemic effects of extra exercise are best made by increased food intake for patients taking *insulin mixtures*, as the mixtures do not lend themselves to as accurate predictions as when the insulins are injected separately. In these cases it is a good practice to take an apple, or an extra glass of milk and 5 soda crackers, or a banana at the meal preceding the exercise, or this nourishment can be taken advantageously just before or, less favorably, during the exercise, and the meal subsequent to the exercise should not be delayed.

Profound hypoglycemic reactions are likely if these measures are ignored by patients taking large amounts of insulin.

**Care of the Skin.** With good control of the diabetes these patients are no more subject to disorders of the skin than are nondiabetic individuals. Emphasis is, however, given to the need for good hygiene—plenty of soap and water daily and meticulous attention to the cleanliness of underclothing. The male subject is advised against having barbers shave the back of his neck because it is believed that this practice increases the incidence of furunculosis and of carbuncles. Two patients seen recently had carbuncles—one on the back of the neck and one on the scalp. Each was due to *Staphylococcus aureus* organisms which were completely resistant to penicillin—clinically and by laboratory testing. Though the antibiotic therapies have proved of immense value in coping with these complications we still consider them among the serious dangers to the diabetic.

**Care of the Teeth.** Thorough cleansing of the teeth with an ammoniated dental powder after each meal and at bedtime will go far in counteracting the predisposition which diabetic patients have to the development of dental cavities and gingivitis. Proper nutrition is also important in this respect. A dental survey, every six months, is recommended.

**Care of the Feet.** The impoverishment of the circulation in the feet of diabetic patients who are past middle age is so common that special care of the feet is necessary to prevent complications, particularly gangrene. In addition to the control of the diabetes preventive measures include:

A. Foot hygiene
B. Avoidance of injury
C. Callus formation and corns—correction and prevention

D Epidermophytosis—prevention and treatment

E Special measures

*A Foot Hygiene* 1 *Take a warm (never hot) foot bath each evening* Dry feet gently but thoroughly and especially between the toes with a soft absorptive towel

2 Anoint the feet with toilet lanolin after bathing once to three times weekly *sufficient to keep the skin soft* Substitute rubbing alcohol for the lanolin if the skin becomes too soft

3 Cut the toenails straight across even with the ends of the toes—never short and never cut back at the sides

4 *Once weekly the feet should be powdered*—with talcum or if there is a predilection to epidermophytosis a film of fungicidal foot powder is rubbed in gently and some is carefully dispersed between the toes The treatment for epidermophytosis is discussed on page 194

*B Avoid injury to the toes and feet* 1 *Exercise care in cutting the nails*

2 Wear comfortably fitting shoes made of soft leather

3 Never place the foot on the floor except in a shoe or slipper

4 Use care in the treatment for corns and calluses

5 *Never apply hot water bottles heating pads or other external heating* appliances to the feet

6 Avoid irritating medicaments to the feet especially iodine phenol and proprietary preparations for removing corns and calluses

7 Prevent and correct epidermophytosis

8 Avoid hose with raised seams

9 Break in new shoes very gradually—one hour daily at first

Corrective measures dealing with (C) Calluses and Corns (D) Epidermophytosis and (E) Special Measures—Buerger's exercises passive vascular exercise ligation of veins and the immersion of hands and arms in hot water—for improving circulation of the feet will be dealt with in the prevention of gangrene page 189

**Cautioning of Patients Against Unsubstantiated Claims** Patients with diabetes are prone to scrutinize news releases on medical subjects in the hope for some advance in the treatment for diabetes Patients are cautioned against premature conclusions—sometimes on the part of the original author but usually on the part of the press Also claims made by manufacturers of proprietary products often lack substantiation In one instance honey was expounded as having curative value for the diabetic Special brews of one kind or another crop up from time to time for which great claims are made but which to date have not benefited diabetic subjects

Patients may need to be reminded that they have an adequate diet and with insulin the diabetes can be controlled even under the most adverse circumstances With th[illegible] concrete mea[illegible] hand they can afford to wait for the com[illegible] of new [illegible] *y chance one of these*

turns out as one might hope for, nothing has been lost. Furthermore, dangers, false hopes, expense and disappointments will have been avoided.

The great desire for a remedy that will be effective when taken orally is easily understood. However, as yet *there is no substitute for insulin and insulin is not effective when taken by mouth.*

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CHAPTER XV

# Complications of Diabetes

## INTRODUCTION

*Chronic complications*, notably degenerative disturbances of the vascular and nervous systems and of the kidneys, present problems of a nature quite different from those of acute complications They cause no appreciable change in the severity of the diabetes The real problem is that these *chronic complications are common and that once established they tend* to progress, and it is they, and not the diabetes *per se*, that incapacitate and threaten life The measures recommended in dealing with these chronic degenerative disorders pertain to good control of the diabetes month after month and year after year, to suitable changes in diet, and to preventive *and corrective procedures that may be indicated in the individual case* These features are dealt with under their respective headings elsewhere in this chapter

Nondegenerative disorders of a chronic nature which complicate diabetes are, in general, treated as in the nondiabetic with appropriate adjust*ments to insure adequate control of the diabetes*

Every diabetic patient will have an *acute complication* sooner or later Whether it is an acute appendicitis, tonsillitis, carbuncle or other acute disturbance, the treatment that is satisfactory under usual conditions abruptly becomes inadequate The blood sugar increases in concentration *above normal and large amounts of sugar are lost in the urine* The anorexia so common during acute febrile episodes may lead the uninformed to omit insulin at such times This mistake may lead to grave dangers

Too much emphasis cannot be put on, *first*, the unfavorable effect which most acute complications have on the diabetes Even the patient who ordi*narily does not need insulin may suddenly—within* a matter of hours—present the indications for emergency insulin therapy A good illustration of this is the obese diabetic patient, E D, a synopsis of whose case record is presented on page 236 This patient with a mild diabetes developed diabetic coma during an acute infection and was in a perilous condition *requiring 1750 units of insulin in the first* twenty four hours of treatment The *second* feature of acute complications is also illustrated by this case namely, that as the acute complication subsides the severity of the diabetes

is reduced and, in this case, satisfactory control of the disorder was maintained without insulin *Thirdly*, good control of the diabetes is an important aid in overcoming the acute complication and it makes complete return to the pre-complication status of the diabetes more certain than if the diabetes is allowed to remain out of hand during the acute episode *Fourthly*, the ease with which even the most severe case of diabetes can be controlled during these trying periods is to be emphasized

It is not true that the diabetes cannot be controlled during acute complications It is not true that poor control of the diabetes does not alter the outlook in an unfavorable manner It is not true that diabetic patients are unfavorable risks nor that they respond less well than nondiabetic patients to sulfa or antibiotic therapy Recognizing these principles the physician who is familiar with the need to alter the diet and its distribution and to adjust the insulin therapy, as the indications for these changes will arise will tide the diabetic patient through acute crises with very little if any more risk than if the patient were not diabetic.

An illustrative case is presented on page 209, depicting the methods of therapy employed at the Pennsylvania Hospital Separate sections are devoted to the problems presented by other complications of an acute nature, notably pregnancy, infections surgical conditions and diabetic coma

## CHRONIC COMPLICATIONS

### I *Degenerative Vascular Lesions*

Three distinct abnormalities, usually grouped under the heading of arteriosclerosis are especially common in the diabetic population and appear at an earlier age than in nondiabetics These are (a) *atherosclerosis*—essentially a disease of the intima (b) *calcification of the arterial walls* (*Monckeberg's sclerosis*) and (c) *arteriolarsclerosis* All grades of involvement from minimal to extensive changes of an advanced nature are seen These three subcategories of arteriosclerosis are apparently independent of each other any one may occur singly or they may be combined in the same patient However, whatever underlying processes are at work, all three are commonly associated with diabetes and especially diabetes that has not been well treated and is of long duration These changes are apt to appear at an early age—in the twenties—and far outstrip in progressiveness similar changes seen in older nondiabetic individuals The early start the speed with which the degenerative processes progress and the advanced degree of the degenerative changes in the diabetic patient are in contrast with the later onset, the slow progress, and the lesser degree of the same disorder in nondiabetic individuals.

The incidence of advanced and incapacitating arterial disease is increasing at an alarming rate This increase is attributed to the prolonged

CHAPTER XV

# Complications of Diabetes

## INTRODUCTION

*Chronic complications,* notably degenerative disturbances of the vascular and nervous systems and of the kidneys, present problems of a nature quite different from those of acute complications. They cause no appreciable change in the severity of the diabetes. The real problem is that these chronic complications are common and that once established they tend to progress, and it is they, and not the diabetes *per se,* that incapacitate and threaten life. The measures recommended in dealing with these chronic degenerative disorders pertain to good control of the diabetes month after month and year after year, to suitable changes in diet, and to preventive and corrective procedures that may be indicated in the individual case. These features are dealt with under their respective headings elsewhere in this chapter.

Nondegenerative disorders of a chronic nature which complicate diabetes are, in general, treated as in the nondiabetic with appropriate adjustments to insure adequate control of the diabetes.

Every diabetic patient will have an *acute complication* sooner or later. Whether it is an acute appendicitis, tonsillitis, carbuncle or other acute disturbance, the treatment that is satisfactory under usual conditions abruptly becomes inadequate. The blood sugar increases in concentration above normal and large amounts of sugar are lost in the urine. The anorexia so common during acute febrile episodes may lead the uninformed to omit insulin at such times. This mistake may lead to grave dangers.

Too much emphasis cannot be put on, *first,* the unfavorable effect which most acute complications have on the diabetes. Even the patient who ordinarily does not need insulin may suddenly—within a matter of hours—present the indications for emergency insulin therapy. A good illustration of this is the obese diabetic patient, E. D., a synopsis of whose case record is presented on page 236. This patient with a mild diabetes developed diabetic coma during an acute infection and was in a perilous condition requiring 1750 units of insulin in the first twenty four hours of treatment. The *second* feature of acute complications is also illustrated by this case, namely, that as the acute complication subsides the severity of the diabetes

is reduced and, in this case, satisfactory control of the disorder was maintained without insulin *Thirdly*, good control of the diabetes is an important aid in overcoming the acute complication and it makes complete return to the pre complication status of the diabetes more certain than if the diabetes is allowed to remain out of hand during the acute episode *Fourthly*, the ease with which even the most severe case of diabetes can be controlled during these trying periods is to be emphasized

It is not true that the diabetes cannot be controlled during acute complications It is not true that poor control of the diabetes does not alter the outlook in an unfavorable manner It is not true that diabetic patients are unfavorable risks nor that they respond less well than nondiabetic patients to sulfa or antibiotic therapy Recognizing these principles, the physician who is familiar with the need to alter the diet and its distribution and to adjust the insulin therapy, as the indications for these changes will arise will tide the diabetic patient through acute crises with very little, if any, more risk than if the patient were not diabetic

An illustrative case is presented on page 209, depicting the methods of therapy employed at the Pennsylvania Hospital Separate sections are devoted to the problems presented by other complications of an acute nature notably pregnancy, infections, surgical conditions and diabetic coma

## CHRONIC COMPLICATIONS

### I *Degenerative Vascular Lesions*

Three distinct abnormalities, usually grouped under the heading of arteriosclerosis, are especially common in the diabetic population and appear at an earlier age than in nondiabetics These are (a) *atherosclerosis*—essentially a disease of the intima, (b) *calcification of the arterial walls* (*Mönckeberg's sclerosis*) and (c) *arteriolarsclerosis* All grades of involvement from minimal to extensive changes of an advanced nature, are seen These three subcategories of arteriosclerosis are apparently independent of each other—any one may occur singly or they may be combined in the same patient However, whatever underlying processes are at work, all three are commonly associated with diabetes and especially diabetes that has not been well treated and is of long duration These changes are apt to appear at an early age—in the twenties—and far outstrip, in progressiveness, similar changes seen in older nondiabetic individuals The early start, the speed with which the degenerative processes progress and the advanced degree of the degenerative changes in the diabetic patient are in contrast with the later onset, the slow progress, and the lesser degree of the same disorder in nondiabetic individuals

The incidence of advanced and incapacitating arterial disease is increasing at an alarming rate This increase is attributed to the prolonged

life span of the diabetic The average life span in the Naunyn era was 44 5 and in the Best era, 64 5 years [1] This is undoubtedly part of the answer but other factors associated with diabetes are at work, factors which so far, have defied unraveling It is into this field that most intensive research activities should be directed A basis upon which to appraise improvement or other change, will be established if a most careful evaluation of the arteriosclerotic status, in its broadest aspects, is made in every case This will involve especially a most careful *history* dealing with symptoms and functional capacity, *retinoscopy, blood pressure determinations*, notation of the *degree of thickening of the palpable arteries*, the *extent of the cardiac borders*, preferably determined by fluoroscopy and recorded by roentgen ray pictures, *electrocardiogram, evaluation of the circulation of the feet* (see p 181), and a *roentgen ray search for calcified vessels* A tourniquet test will often detect undue *capillary fragility*—especially in patients having retinal hemorrhages A recording of the *blood cholesterol* (venous blood with patient in fasting state) may be of value for comparative purposes The presence or absence of *albuminuria* should be noted and also the range of the *specific gravity of sugar free urine* The *blood urea nitrogen* concentration is determined if albuminuria and arterial hypertension are present

**Arteriosclerosis Obliterans (Atherosclerosis).** The changes in the intima of the arteries which characterize this disorder make it the outstanding vascular complication of diabetes Intimal plaques form on the side of the medium sized arteries causing a localized narrowing of the lumen which predisposes to occlusion especially of the coronary arteries and the arteries of the distal extremities hence the term *arteriosclerosis obliterans* which, because of its descriptive connotation, is receiving general adoption

The obliterative nature of the atheromatous changes by reducing the size of the lumen of the artery, reduces the capacity of the vessel to deliver blood to the peripheral tissues in normal amounts Varying degrees of obliteration may exist for long periods without causing symptoms but, as the lumen of the artery is progressively infringed upon, eventually symptoms, notably anginal pains and intermittent claudication are noted on occasions of increased physical activity Still later, the patient becomes more and more conscious of the impaired circulation as indicated by coldness and disturbances in sensation in the feet, and finally with complete occlusion, localized death of tissue occurs This is exemplified in the case of myocardial infarction or of gangrene of an extremity

The precipitation of the acute complication is usually on the basis of a thrombus occurring in the vessel where its wall is deformed by eccentric atheromatous plaques Insufficiency of the coronary circulation and gangrene are dealt with under acute complications (see p 212)

The mechanisms associated with these changes are more readily under

stood if it is realized that arteriosclerosis is not a static condition but one with periods of exacerbation and periods of quiescence It comprises localized intimal thickening in which necrosis takes place and cholesterol and other lipids are laid down in the diseased site These subsequently are dissolved out, leaving clefts The resulting softened mass is the so called *atheroma* The atheroma is subject to cellular exudation, vascularization of the margins organization and, in the advanced lesion, hemorrhage Destruction of the media occurs in advanced cases and calcification of the plaque is common Atherosclerosis bears a direct relationship to *obesity, to the duration of the diabetes and to hypercholesterolemia with poorly controlled diabetes*

**Monckeberg's Sclerosis.** Calcification of the media of the muscular arteries is the salient feature of Monckeberg's sclerosis It is not as common as atherosclerosis in diabetic patients but is seen more frequently and in more advanced stages in these patients than in nondiabetic individuals It gives to the palpable artery a beaded contour of stony hardness —the so called pipestem artery Calcification of the media may occur in any artery but involvement of the vessels of the distal extremities is the most common

**Arteriolarsclerosis** In this form of arteriosclerosis hyaline material is laid down in the walls of the arterioles as described on page 62 It, also, occurs more frequently and at an earlier age and to more severe degree in diabetic than it does in nondiabetic subjects Of diabetic patients over fifty years of age arteriolarsclerosis involving renal vessels is present in 77 6 per cent or about five times as frequently as in nondiabetic controls Arterial hypertension is more constantly associated with arteriolarsclerosis than it is with atherosclerosis

*Treatment for Chronic Degenerative Vascular Complications of Diabetes* The chief aim in treating patients having chronic degenerative changes in the vascular system is to restore disturbed physiologic processes to normal, or as nearly to normal as is practicable, and in this manner provide relief from or reduce as much as is possible, the subjective symptoms and clinical evidences of the disease In so doing it is hoped that the tendency of the disorder to become worse will be allayed

*Correction of Disturbed Physiologic Processes* Disturbances in the physiologic processes and the practicable means of dealing with them are as follows

1 HYPERGLYCEMIA AND GLYCOSURIA The treatment is as outlined on page 103, except that it is advisable to adjust the diet and insulin more conservatively than in patients having minimal or no demonstrable changes in the vascular system A gradual decrease of the hyperglycemia—over a period of several weeks—is preferable to rapidly attained control Hypoglycemic reactions should be guarded against, as they predispose to occlu

sion of the coronary arteries in these patients Fortunately, these patients usually have a wide margin of safety permitting *good control of the diabetes* without undue risk of hypoglycemic reactions

2 HYPERCHOLESTEROLEMIA AND EXCESSIVE *CHOLESTEROL ESTERS AND* LIPEMIA The high incidence of insufficiency of the coronary arteries in nondiabetic patients who have hypercholesterolemia *and those who have* xanthomatosis emphasize the part that like disturbances in physiology may play in the presence of diabetes A reduction of the lipid *transport in the* blood is most readily achieved (a) when obesity is corrected and (b) when a liberal carbohydrate intake is permitted *Allowances of 250 to 335 gm* of carbohydrate in the daily diet usually are necessary to reduce the hyper cholesterolemia appreciably and to reduce the metabolism *of fat sufficiently* to overcome the hyperlipemia A low intake of fat—below 75 gm, and preferably below 50 gm daily—is desirable It is *probable that when the* complicated and variable mechanisms involved are solved it will be all too obvious that most diets, recommended by authorities on diabetes, contain too little carbohydrate and too much fat (c) We advocate protein in excess of 100 gm

3 OBESITY Correction of obesity will tend to prevent as well as alleviate the progressiveness of the degenerative changes in the arteries It is accomplished as outlined on page 105 except that when advanced arterial disease exists it is preferable to permit as liberal an intake of carbohydrate as is practicable, e g, 250 gm in a diet containing 100 gm of protein and 1700 calories Circulatory difficulties are much more common in the over weight than in individuals of normal weight Atherosclerosis is most common in the obese and relatively uncommon in those who are underweight, and undernutrition militates against the development of the complication in man and tends to protect experimental animals who are not so protected if in a well nourished state Also, based on autopsy evidence, a thin subject of fifty years of age usually has less atherosclerosis than a forty year old fat person (Wilens)[2] Wilens has shown that a reduction in body weight causes regression of atheromatous changes and a reduction of the lipid content of atheromatous plaques in a significant percentage of cases The state of nutrition plays an important, if not an essential, part in the speeding up and slowing down of this serious complication of diabetes An optimum state *of nutrition with the body weight a trifle below the* standard weight after thirty five years of age is a goal aimed at too infrequently and much less frequently is it attained

The red[illegible] *in body weight* in cases of [illegible] favorable influence on high [illegible] the diabetes has, in *our ex*[illegible] on arterial hypertension in [illegible] diabetic than it has in nondiabetic patients The correction of *hypertension* is of special value in subjects with atherosclerosis and arteriosclerosis Uncorrected, the hypertension accelerates these degenerative *processes*

*Restriction of the salt intake* is of outstanding value This measure attains even greater importance if the hypertensive obese diabetic patient displays evidences of circulatory decompensation The benefits of this measure were observed in 1926 in dealing with circulatory failure in nondiabetic subjects [3]

Thoracolumbar sympathectomy is recommended when the indications for it are clear These are

1 The patient is not over fifty years of age
2 There are clear evidences that the hypertension is progressive
3 There is no nitrogen retention in the blood
4 The heart is not markedly enlarged certainly not more than a 50 per cent increase above the normal dimensions and with no evidences of congestive heart failure
5 The responses to amytal cold pressor (if applicable) and tetra ethyl ammonium chloride (etamon) tests, and the exclusion of a pheo chromocytoma by the dibenamine hydrochloride and benzodioxane tests indicate that one can reasonably anticipate a beneficial outcome Good results and vice versa have followed despite poor responses to these tests but in general they give valuable impressions as to the course to pursue
6 When responses to conservative treatment—reduction of the obese salt free diet mild sedation and psychiatric therapy—are unsatisfactory
7 When a complete clinical appraisal indicates that the patient without a sympathectomy has a life expectancy of not more than five years

These may appear to be severe terms upon which to decide concerning a sympathectomy but if adhered to needless sympathectomies will be avoided and on the other hand the patient who derives little or no benefit from other therapies and is a fit subject for operation will not be deprived of the possible advantages which it has to offer It has been estimated that approximately 4 per cent of hypertensive patients are suitable candidates for sympathectomy

## II *Diseases of the Coronary Arteries Complicating Diabetes*

Occlusion of the coronary arteries has far outstripped other causes of death in diabetic patients at the Pennsylvania Hospital The frequency of this serious complication is as frequent indeed in the past two years has been more frequent in the female than in the male diabetic patients This is of great interest as, in the nondiabetic population this complication occurs in male and female between the ages of fifty one and sixty in approximately a 5 to 1 ratio [4] There is an increasing incidence of diseases of the coronary arteries in diabetics and especially is this true for the female patients At one time during the past year we had on a general medical ward of forty beds, five female diabetics each with an occlusion of a coronary artery Each was overweight four were known to have had increased

arterial blood pressure, one had no previous history of diabetes, and four patients had a long standing uncontrolled diabetes

The main known factors at work in increasing the prevalence of disease of the coronary arteries in diabetic patients are (1) the extended *duration of the diabetes*, the *degree of severity* and *control* of the diabetes —mild diabetes of short duration is not as likely to be complicated by occlusive disease of the coronary arteries as when the disease is of long duration, of a severe degree and poorly controlled (2) The increased span of life for diabetics has influenced unfavorably the incidence of disease of the coronary arteries (3) *Excessive concentration of cholesterol* and *other lipids* in the blood is associated with *a much higher frequency of atherosclerotic* changes and occlusive phenomena than when these chemical abnormalities are absent (4) *Arterial hypertension*, (5) *obesity*, (6) *excessive use of tobacco* and (7) *hypoglycemic reactions* predispose to occlusion of the coronary arteries which have undergone marked atherosclerotic changes It seems most probable that this is the result of an "alarm reaction" and bears a relationship to the increased amount of epinephrine in the circulation which occurs with the development of a hypoglycemia

Patients with occlusive disease of the coronary arteries are predisposed to sequelae similar to those seen in the nondiabetics but the sequelae are likely to appear earlier and they tend to be more rapidly progressive in diabetic individuals They include myocardial decompensation heart block, auricular and ventricular fibrillation, complete occlusion of a coronary artery, and embolism

There is no satisfactory yardstick with which to measure the efficacy of prophylactic measures in the individual case but it is our impression that benefit accrues from control of the diabetes, from reduction of hypercholesterolemia through the agency of liberal carbohydrate and protein and low fat allowances in the diet, from the correction of obesity and hypertension, from the restriction or complete elimination of the use of tobacco and by practicing great care in preventing hypoglycemic reactions

An understanding internist who has a comprehensive knowledge of the patient's problems, mental and physical, is in the best position to give effective reassurance and guide the patient into gracefully accepting the situation in which he finds himself and in helping him institute an optimum regimen of living

*Treatment* Insufficiency of the coronary circulation may be manifest by attacks of *angina pectoris*, the treatment for which comprises

1 Gradual control of the diabetes—this takes several weeks if the risk that attends rapid control is to be avoided

2 The correction of obesity A low calorie diet is employed and when the weight has reached a satisfactory level, the diet is increased, using liberal protein and carbohydrate with low fat contents, e g, protein 90 gm, carbohydrate 275 gm, and fat 59 gm (1900 calories)

3 Vasodilators—nitroglycerin, 0 3 mg (1/200 gr) and aminophylline,

0.5 gm (7½ gr) are most commonly used for the alleviation of an attack of angina pectoris. Patients who are subject to attacks of angina should never be without nitroglycerin, which may also be used as a prophylactic measure when the patient's attack pattern is known. To prevent recurrent attacks the following remedies are recommended: theobromine calcium,* 0.5 gm (7½ gr) and phenobarbital, 10 mg (⅙ gr) four times daily, or papaverine hydrochloride, 60 mg (1 grain) four times daily.

4. Restriction of physical activity—climbing exercises and brisk walking against a strong or cold wind especially are to be avoided. Absolute physical rest during an anginal attack will usually bring relief.

5. The use of tobacco is interdicted.

6. Reduction of the total body metabolism by administering sufficient amounts of 6-propyl thiouracil to keep the basal metabolic rate between minus 10 and minus 25 per cent. Ordinarily this is achieved with 50 mg four times daily, though larger initial amounts may be needed and smaller maintenance doses may suffice. This measure is recommended as an especially satisfactory remedy but its use should be restricted to intractable cases of angina pectoris.

**Acute Occlusion of a Coronary Artery.** The treatment employed at the Pennsylvania Hospital and supplemented by other measures that may be indicated, to give relief from pain, to put the patient at rest mentally and physically, is as follows:

1. Complete rest in bed—patient is fed and not allowed to bathe, or turn or get on a bed pan without help.

2. The diet is liquid, soft or regular as tolerated. It is divided into four equal and small meals as for other acute complications (see p. 217).

3. Mineral oil 30 cc and fluidextract of cascara sagrada, 4 to 8 cc, is given daily at bedtime if needed for daily evacuation.

4. Papaverine hydrochloride, 60 mg (1 grain), is given orally every four hours.

5. Morphine sulfate is used in amounts sufficient to provide relief from pain—usually 15 mg (¼ grain) or 30 mg (½ grain), given hypodermically.

6. Heparin, 50 mg, is given at once intravenously and repeated every six hours until the Dicumarol therapy† has reduced the prothrombin time to 30 to 20 per cent of normal.

7. Dicumarol is administered orally as follows:

300 mg on the first day.
200 mg on the second and third days.
50 to 300 mg daily thereafter as needed to maintain a prothrombin time between 20 and 30 per cent of normal until ambulation is permissible—usually three to five weeks—at which time the anticoagulant therapy is discontinued.

* Commercially available as Purital and Purobarb—both supplied by A. J. Parker Company, Philadelphia.

† A more rapidly effective anticoagulant, Tromexan—a brand of ethyl biscoumacetate—is showing considerable promise and may replace Dicumarol.

*Studies* 1 Prothrombin time is determined daily until the patient's tolerance to Dicumarol is known Thereafter the test is done on alternate days or every third day

2 An electrocardiogram and an erythrocyte sedimentation rate are secured at weekly intervals

3 *Close clinical observation*—several times daily Readings of the blood pressure are taken twice daily until convalescence is under way

*Reduction of the body weight*, while reparative mechanisms are at work is not recommended but when convalescence is well established—usually four or five weeks after the acute onset, a reduction program is advised for the patients who are overweight

Treatment for the diabetes during the acute phase is the same as for an acute infection (see p 217), until the patient is free from pain and can adopt a regular meal schedule

## III *Circulatory Disturbances in the Legs and Feet*

*Appraisal of the Circulation* Failure of the arterial circulation to deliver adequate amounts of blood to the tissues results from a narrowing of the arterial lumen as occurs frequently in the peripheral vessels of the older diabetic patients Arteriosclerosis obliterans occurs eleven times more frequently in diabetics than in nondiabetic controls [5]

The evaluation of the circulation is in reality the determination of the degree of patency of the lumen of the artery at its narrowest point and it is upon this feature that the prognosis and therapy depend

*Symptoms* Mild degrees of arteriosclerosis obliterans cause no symptoms but as the condition progresses the sensation of *coldness* in the affected extremity becomes apparent *A decrease in the muscular endurance* and impaired sensitivity to minor injuries and an accompanying partial anesthesia appear subsequently The symptoms of neurologic origin are to be evaluated carefully if the pitfall of attributing a diabetic neuritis to a deficient circulation and not to a more widespread diabetic neuropathy is to be avoided The physical signs of circulatory inadequacy must support the diagnosis of an ischemic neuritis Otherwise, the symptoms are more likely to be due primarily to metabolic degenerative abnormalities in the nerves as occur in the neuropathies associated with diabetes (see p 202)

*Intermittent claudication*, first appearing after brisk walks for considerable distances, appears as a frequent symptom A severe grade of arterial obstruction is present when this symptom is provoked by walking 20 to 30 yards and at a slow pace If comparative studies are being done from time to time, the same distances and speeds in the various observations are maintained A short rapid walk will provoke intermittent claudication when a slow walk for a long distance may not be accompanied by this distressing symptom

*Pain*—severe and persistent—*in the feet* and *especially in the digits*

*while at rest*, and especially at night, indicates advanced vascular obstruction, provided neuropathic changes are not responsible The onset of rest pain may be insidious and progress gradually or it may be sudden with the complete occlusion of an artery Rest pain is common in the region of an ulcer or of a gangrenous area

Pain due to an ischemic neuritis is of wider distribution and the discomfort is variable in nature and intensity and has burning or shooting characteristics

The onset of pain in an extremity having a poor circulation may follow a minor injury to the foot In this case the local reaction exerts a demand for circulation which the circulatory means at hand is unable to meet The situation may be made worse by local vasoconstriction This is a common occurrence preceding the appearance of gangrene although gangrene may appear spontaneously with or without pain Frequently a vesicle is the first local sign of gangrene

*Physical signs* On *inspection* the dependent limb with a normal circulation shows no discoloration but with advancing arteriosclerosis obliterans the affected member becomes bluish red when in the dependent position This discoloration fades proximally over the dorsum of the foot but in some cases it extends halfway to the knee or even higher The prompt change to a cadaveric pallor following the elevation of the foot for two minutes and a slow—in excess of thirty seconds—return of the cyanosis on returning the foot to a dependent position, combine to indicate an advanced degree of obstruction in the arteries These postural changes are highly significant when present The development of collateral circulation may prevent these color changes even though the large vessels are pulseless It is significant that arteriosclerosis obliterans involves chiefly the larger vessels and it is not infrequent that the capacity for arteriolar dilatation is not greatly impaired Marked pallor may follow the sudden occlusion of an artery of medium size

*Trophic changes* in the skin, muscles and nails may be apparent on inspection Ulceration and gangrene with or without apparent infection may be present Evidences of a pyogenic infection, a lymphangitis and of *epidermophytosis* are important Local injuries, and especially fissures that result from fungus infections afford a ready portal of entry for other infective agents

*Gangrene* involves the more prominent parts of the feet as a rule—the toes, the heel the prominence of the metatarsophalangeal joints of the small and great toes the dorsum of the foot and the malleolar regions

*Palpation* The tips of the toes are cold in advanced degrees of obliterative arteriosclerosis The involved foot may be cold in contrast to its fellow A difference in temperature in the two feet is especially significant when both have been exposed to the same environmental temperature Whether this coldness is due to a functional or organic obstruction is determined

by special studies of the skin temperature It is important to detect impaired or absent pulsations in the dorsalis pedis, *posterior tibial, popliteal* and femoral arteries Pulsations of the dorsalis pedis arteries may be absent because of congenital anomalies *but if, in addition,* the posterior tibial and popliteal pulsations are impaired or absent, arteriosclerosis obliterans is *almost certain to be the cause We consider the degree of pulsation and changes in temperature of the tips of the toes as the most important of the clinical means of appraising the circulatory efficiency of a limb* Poor tone of the muscles and impaired or intensified cutaneous sensitivities are among the less specific results of an impaired circulation



Fig 21 Calcification of the arteries and osteoporosis in the feet of a diabetic patient

Ulcers over a joint, or soft corns between the toes are common forerunners of arthritis or osteomyelitis due to pyogenic organisms Careful physical estimation and roentgen ray studies of these possibilities will often explain chronic discharging sinuses and failures in healing

The clinical evaluation of the state of the circulation is superior to special tests The latter have an important place in supporting clinical findings *however In general the circulation is good* if the patient does not complain of pain in the extremities, if there are no color changes, if there is good *pulsation in the dorsalis pedis and posterior tibial arteries*, and if the tips of the toes are warm Warm toe tips in the absence of good pulsation of the peripheral arteries is *a sign of a good collateral circulation* Contrariwise *the circulation in the limb is severely impaired* if rest pain and intermittent claudication are prominent, if the bluish red cyanosis *(rubor)* of the dependent foot gives way to a cadaveric pallor when the foot is elevated, if the tips of the toes and the foot are persistently cold and *if there is* ab

sence of pulsations in the peripheral arteries of the foot—the dorsalis pedis and posterior tibial arteries

*Special Tests* These studies are used selectively when needed to support clinical impressions Usually they are not necessary

ROENTGENOGRAPHY This study aids in determining the degree of and position of calcified areas in the arterial wall It should include not only the foot and leg but also the thigh, as obstructive lesions in the femoral arteries are frequent Patchy, dense deposits of calcium causing a marked degree of obstruction, identified by roentgen ray studies, may in some cases influence the selection of the site of amputation

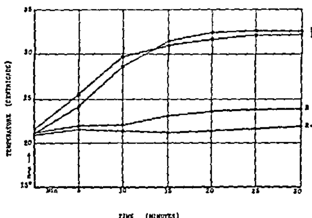



Fig 22 Skin temperature vasodilatation test The increase in temperature in the left foot upon immersion of the hands and arms in hot water indicates a high degree of spastic vasoconstriction The absence of a similar response in the right foot is indicative of organic vascular occlusion

Roentgenograms are of value also in detecting osteomyelitis of the small bones of the feet and in assaying the degree of osteoporosis and destruction of bone in the rare case of neurotrophic foot (see p 207)

SKIN TEMPERATURE STUDIES These studies tend to (a) confirm the clinical diagnosis and (b) afford information regarding the relative degree of functional arterial spasm and of organic arterial occlusion The temperatures of the skin over the tips of the toes, the dorsum of the affected foot and various other levels are taken the patient having been in a room the temperature of which is approximately 20° C (68° F) for one-half hour These readings are recorded and compared with those taken one hour after both arms and hands have been immersed in hot water, 43 to 45° C. This schedule, as advocated by Gibbon and Landis [9] causes a definite reflex vasodilatation and a rise in temperature in the distal extremities from a normal temperature of about 24 7° C on the toe and 30.2° C on the sole of the foot, to 33 5° or 34 5° C if the vascular supply is normal or if occlusion

has been due to vascular spasm (Fig 22) There is little or no rise in the skin temperature of the feet in the event of an advanced occlusion of the arteries due to organic changes This test is especially desirable if a sympathectomy is considered It identifies the vascular spastic type of occlusion in which the operation holds promise of success in contradistinction to the organic occlusive vascular disease, in which sympathectomy would be not only valueless but dangerous Satisfactory evaluation of the alterations in circulation is obtained without the more radical nerve-blocking procedures, notably spinal anesthesia or the injection of the peroneal nerve Refinements in the execution of this test have detracted from its value and hence are not included

PLANTAR ISCHEMIA TEST This test, popularized by Samuels,[7] is carried out with the patient in the reclining position The patient raises the foot being studied to an angle of 45 degrees, in which position he flexes and *extends the foot rapidly for one minute Obstructive arterial disease of a* severe degree is indicated by the development of an alabaster like color of the plantar surface of the foot There is little or no change in color if the arterial circulation is normal This test when positive indicates a slowing of the circulation as does the *elevation* and *dependency* test presented on page 185

*Other Tests* Oscillometric studies, arteriography, histamine flare test intradermal saline wheal test and the fluorescein test are listed because they appear in medical writings frequently and not because of their clinical value We do not employ them because they either add little or no information and are unnecessary, or mislead or carry risk out of proportion to the information they might reveal We do not mean to detract from the value of these tests as research procedures

*Differential Diagnosis Arteriosclerosis obliterans as it is encountered* in diabetes characteristically develops occlusive manifestations in patients over forty years of age it involves the lower extremities almost entirely, thrombophlebitis is not a feature of the disorder, there is calcification of the arteries in 69 per cent, males constitute 83 per cent of those afflicted,[8] 34 per cent have an associated hypertension, 20 per cent of Allen's patients had diabetes, and elevated blood lipids is a common finding

In contrast thrombo angiitis obliterans, with which arteriosclerosis obliterans might be confused, practically always occurs in male subjects under fifty years of age, 40 per cent have involvement of the upper extremity, 40 per cent have thrombophlebitic phenomena, there is no *calcification* of the arteries, diabetes is a rare complication and the blood lipids are usually normal

*Diabetic neuropathy may co exist with arteriosclerosis* obliterans but numbness, lightning pains and ulcerations may be due to neurotrophic changes in the presence of warm toe tips and excellent pulsation of the *peripheral arteries* Absent or sluggish tendon reflexes and an impaired

vibratory sense over the distal extremities afford valuable clues in identifying the neurologic nature of the disorder in contrast to the predominantly vascular changes already presented

There should be no difficulty in differentiating *gout, arthritis, sciatica, the burning feet of malnutrition states, erythromelalgia* and *thrombophlebitis* if the history is carefully taken and if the physical examination is complete

### IV *Gangrene*

Gangrene in an extremity of the diabetic patient occurs primarily because of the occlusive nature of arteriosclerosis obliterans (Fig 13) and the resulting incompetency of the arterial circulation in meeting sudden or increased circulatory demands The precipitating cause of gangrene is usually injury which may be due to trauma, infection or extremes of temperature Thrombotic or embolic phenomena in an atheromatous vessel also may be the exciting cause of gangrene Any combination of events that will increase the need for circulation or that will obstruct the supply route is sufficient to deprive the tissues of nutrition adequate to retain their viability

The onset of gangrene may be sudden and painful, as occurs in the abrupt cutting off of the circulation by an arterial embolus Or, there may be no pain and a vesicle may be the first ominous sign of local capillary damage to be followed by changes in color from the normal to a dark blue-gray or black in the underlying tissues Infection, with its complicating hyperemia and lymphangitis, is a common complication It may progress rapidly or slowly and the speed with which local death of tissues proceeds as a result of infection will depend on the degree of the devitalization of the tissue and the virulence of the infection Infection tends to cause local inflammatory changes with an exudative lesion and accounts for more pain than is usually the case when infection is absent In the latter instance the gangrenous area may be relatively painless and become demarcated, hard, dry, mummified shriveled and black

In appraising the clinical state of a diabetic patient who has a gangrenous area special attention is given to the degree of concomitant degenerative changes, notably in the coronary cerebral renal and retinal circulations These patients are usually over fifty years of age and have degenerative changes in their arteries of a degree seen in control nondiabetic subjects who are at least ten years older

**Prevention** More often than not arteriosclerosis obliterans is present to an advanced degree when these patients seek treatment Nevertheless, there will be ample opportunity to practice prophylaxis though it is not always as successful as we would have it be The preventive measures are

A *Control of the Diabetes*

B *Correction of Hypercholesterolemia if Possible* For this purpose

eral amounts of carbohydrate (250 to 335 gm) with low fat (less than 75 gm) and ample protein (5/8 gm per pound of the ideal body weight) are allowed

C *Weight Regulation* It is necessary to secure and maintain a body weight a trifle below the standard weight

D *Special Care of the Feet* Details on hygienic care of the feet are dealt with in some detail on page 173

E *Symptomatic Relief from Pain*

F *Local and Systemic Treatment for Ulcers and Infections* In addition to local therapy bacterial cultures are taken from ulcerating areas and from discharging sinuses and the sensitivities of the pathogenic organisms to the various antibiotic agents are determined This measure usually permits a specific attack on the offending organisms Too much emphasis cannot be placed on the value of complete bacteriologic evaluation of these infections Lives and limbs will be saved if such studies are done in every case of bacterial infection Furthermore, cultures of the blood are taken if the patient is febrile and has an increase in the number of leukocytes in the blood

G *Physical Therapy* The circulation in the legs and feet may be improved by the following measures (1) Sanders oscillating bed, (2) intermittent suction and pressure, (3) intermittent venous occlusion, (4) Buerger s exercises, (5) application of heat to hands and arms, and (6) thermo regulated foot cradles *Applications of heat, without appropriate automatic thermoregulation, to the legs and feet are contraindicated* Probably no other single exciting cause of gangrene outnumbers that of the unwise application of heat Heat, under normal conditions, causes vasodilatation and hyperemia in the limb but with an impoverished circulation it does not exert this effect but rather tissue damage occurs, probably due to a local increase in the tissue metabolism without a commensurate increase in the circulation

SANDERS OSCILLATING BED [9] This is the most satisfactory form of the mechanical methods of therapy The treatment may be continuous or intermittent, e g, one hour three times daily depending upon the degree of relief from pain that is achieved This form of therapy is contraindicated in the presence of a bacterial infection with a cellulitis

SUCTION AND PRESSURE THERAPY [10] This method* has suffered in popularity in recent years but is nevertheless helpful in some cases It is contraindicated in the presence of collections of purulent material acute bacterial infections and cellulitis Suction amounting to 80 to 120 mm of Hg is applied for twenty five seconds alternating with a positive pressure of 40 to 80 mm of Hg for five seconds At the outset of the treatment pressures alternating from minus 80 to plus 40 mm of Hg and progressing to minus 120 to plus 80 mm are used according to the relief achieved

* *Equipment is manufactured by* The Burdick Corporation Milton Wis

Treatments are given one to two hours daily, decreasing as improvement is established to three treatments, and finally one treatment per week

INTERMITTENT VENOUS OCCLUSION [11] A cuff is fitted above the knee and is inflated to a pressure of 70 to 80 mm of Hg, obstructing the venous return for one, two or three minutes, followed by a like period of release When a reactive hyperemia occurs appreciable relief from intermittent claudication results The treatment is continued for one to two hours daily It is contraindicated in cases of venous insufficiency

BUERGER'S EXERCISES * The great advantage of this form of therapy is that it can be carried out by the patient without intricate apparatus (Fig 23) at home and for long periods The patient, lying on his back, raises

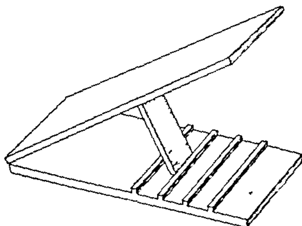


Fig 23 A Buerger board

one or both feet at an angle of 15 to 60 degrees, and allows them to rest on an adjustable board until the feet are quite blanched or until the foot becomes painful This usually requires about one minute if foot exercises are conducted in this position and somewhat longer, up to three minutes, if the feet are passive The patient then assumes the sitting position with the legs hanging over the edge of the bed until a reactionary hyperemia develops or until pain is experienced in the legs or feet After two to five minutes in this position a rest period for about three minutes is allowed in the horizontal position This cycle may be repeated several times daily at first and increased gradually until the exercises last from one half to one hour daily Dramatic improvement is not to be expected

APPLICATION OF HEAT TO HANDS AND ARMS In cases of vasospasm an

* A Buerger board which is adjustable to different angles is made simply by having two boards, each ¾ inch thick 30 inches long and 12 inches wide hinged at one end with a supporting prop between, which is adjustable to fit on various cleats according to the angle desired

appreciable increase in the temperature of the feet follows the application of heat—hot water bath or electric pad—*to the hands and arms.* This is a simple therapy that patients can carry out themselves. Also, this method enhances the value of the suction and pressure therapy *when the two treatments are given simultaneously.*

THERMOREGULATED FOOT CRADLES. Foot cradles without thermostatic controls are dangerous devices and should *not* be used. *However, great relief* is frequently secured by having the feet and legs in a foot cradle, the temperature of which is maintained at 90° F. (32.2° C.)

H. *Vasodilator Drugs.* Several drugs and *several combinations of therapy* are available for trials. Some may be effective in a case in which others give no benefit. In any case most benefit may be anticipated when the element of *vasospasm is great, and least, or no benefit, when organic arterial* obstruction is of a severe grade.

*Nicotinic acid,* 50 to 200 mg. four times daily in conjunction with papaverine *hydrochloride, 0.1 gm. (gr. 1½) three times daily, both given by* mouth, is sometimes surprisingly helpful.

*Tetra ethyl ammonium chloride* (etamon) by blocking ganglia of the *autonomic nervous system has produced the same degree of vasodilatation* as nerve block, spinal anesthesia and sympathectomy.[12] Hence, this drug is used to determine the relative degrees of vasospasm and of organic ob-

given *intravenously in doses of 0.1 to 0.5 gm. The infusion (1 to 5 cc.) is* given very slowly and the patient is kept at rest for one hour after its completion. The same precautionary measures are taken when intramuscular *injections of 0.8 to 1.0 gm. are given—one-half of the dose is given in each* buttock. A marked drop in the blood pressure may follow the injection of etamon within fifteen or twenty minutes, a reaction which can be con*trolled, if need be, by administering ½ cc. of epinephrine subcutaneously.*

This remedy is often effective in improving the circulation and in relieving pain but the benefit is too evanescent to be of clinical value.

*Dibenamine hydrochloride has a blocking action on the sympathetic* nervous system as well as a neutralizing effect on epinephrine in circulation. Both of these actions tend to cause vasodilatation, an effect which *continues from twenty four to ninety six hours. Dizziness and fainting sen*sations may be experienced on rising from the lying to the standing position after the drug is given. These symptoms are associated with a marked reduction *in the blood pressure.*

Dibenamine is available for oral therapy but the intravenous route yields more satisfactory results. In this manner 5 to 7 mg. per kg. of body weight are given in *300 to 500 cc. of normal saline solution.*

*Priscol* is reported to exert a blocking effect upon the sympathetic vas

cular receptors and a direct histamine like effect upon the smaller vessels [33] It is a beneficial drug in cases of vasospasm when administered in doses of 50 mg four times daily—by oral, intramuscular or intravenous routes Our experience with this remedy in the treatment for organic occlusive vascular disease has been small and disappointing

*Tissue extracts*, notably Depropanex, have reputed value in relieving intermittent claudication Depropanex is given daily in doses of 5 cc intra muscularly In a very limited experience with this preparation we have concluded that an equal degree of relief will ensue if patients subject to attacks of intermittent claudication make an inviolable practice of walking slowly

Our experience with *diethyl oxide* (ether) as a vasodilator is nil but a review of the literature leads one to believe that it is of little practical value At best, the vascular drugs give disappointing results when severe grades of organic occlusive arterial disease are present

*Other Measures* The LIGATION OF THE FEMORAL VEINS has in several instances in our experience given abrupt relief from intractable pains and the relief was attended with an increase in the warmth of the skin in the affected extremities This is not a widely used procedure but the response is so striking even in severe grades of arteriosclerosis obliterans that it deserves consideration when conservative measures fail and amputation seems to be the last resort in the attempt to alleviate pain The beneficial response is apparently due to a slowing of the venous return and to an increase of blood in the impoverished area

EXERCISE Mild forms of exercise are helpful Patients with intermittent claudication must, however, be instructed to walk slowly Buerger s exercises are recommended

OCCUPATION Occupation and other activities which present special risk of injury to the feet should be given up in the face of advanced occlusive arterial disease of the legs and feet

SYMPATHECTOMY In carefully selected cases, and in the face of failure of conservative methods to relieve pain and particularly that of intractable intermittent claudication and in cases in which the element of vasospasm is considerable, sympathectomy may offer some benefit We employ this measure infrequently

*Care of the Feet in the Prevention of Gangrene* General hygiene of the feet is dealt with on page 173 Correction of abnormalities, i e., calluses, corns, fungus infections (epidermophytosis), is as follows

CALLUS FORMATION Calluses are corrected by soaking feet each evening in warm, not hot, soapy water for twenty minutes and then rubbing surface tissues off with gauze Measures to prevent subsequent callus formation will depend on the cause e g., corrective supports for poor arches, foot exercises—especially the practice of picking up twenty medium sized marbles with the toes night and morning—and properly fitting footwear, hose and shoes A leather bar across the bottom of the shoe—correspond

ing to the position of the heads of the metatarsal bones—is often helpful in redistributing pressure exerted by the weight of the body

CORNS Corns are caused by improperly fitted hose and shoes Properly fitting footwear is the first requisite of therapy The cornified layer is pared off with great care, preferably by a chiropodist, but at least by an experienced person other than the patient, and one who has good vision, works in a good light and exercises extreme caution against cutting into living tissue Distribution of the local pressure is secured by employing appropriate felt pads 'Soft corns between the toes are dealt with by wearing shoes that do not compress the toes and by keeping the toes separated with lamb s wool "Soft corns" are especially hazardous as osteomyelitis is frequently an early complication

PREVENTION AND CORRECTION OF EPIDERMOPHYTOSIS Good foot hygiene as already outlined (p 173) is essential in dealing with mild *manifestations of epidermophytosis,* as indicated by a macerated or a parboiled appearance of the skin between the toes with itching Control of this disorder is usually secured promptly by applying a thin film of fungicidal foot powder, *containing zinc undecylenate, undecylenic acid and talc** over the affected areas and between the apparently unaffected toes after each bathing until the condition is controlled and thereafter, once weekly

When *fissures* are present the following preparation is applied daily

| | |
|---|---|
| Rx Salicylic acid | 3 5 gm |
| Benzoic acid | 7 0 gm |
| Castor oil | 30 0 cc |
| 95% ethyl alcohol | 180 0 cc |

With correction of the fissure, treatment with foot powder is begun, or resumed

Or, in place of the prescription presented above, a fungicidal ointment† may be used daily

For the *severe cases* with acute vesicular or bullous eruptions and with secondary infections, the feet are soaked in a 1 8000 solution of potassium permanganate for thirty minutes three times daily, for not more than one week As the acute phase subsides the prescription (salicylic acid, benzoic acid, castor oil and ethyl alcohol) included above, or a stronger keratolytic agent such as one half strength Whitfield s ointment, is used until it appears advisable to change to the foot powder for long term therapy and prevention

The prevention and correction of epidermophytosis assume importance of considerable magnitude as measures against the onset of gangrene Untreated epidermophytosis provides portals of entry for secondary infection which is often sufficient to tip the balance unfavorably when the local cir

* Available commercially as Desenex Powder

† Available commercially as Desenex Ointment

culation is adequate in the absence of infection but insufficient to meet the increased circulatory demands that attend an infectious process

**Treatment for Gangrene.** The therapy for gangrene due to occlusive vascular disease in a diabetic is conducted in cooperation with a surgeon who has a special interest in diabetes and who is especially skilled in the management of these patients

Many factors may influence therapy but the most important are (1) the degree of efficiency of the circulation and (2) the presence of infection Conservative nonoperative treatment is justifiable if the area of gangrene is well demarcated and superficial, if the tips of the toes are warm and there is good pulsation in the dorsalis pedis and the posterior tibial arteries, when the extremity retains normal color on elevation and when in the dependent position The first principle is to do no harm The active therapy comprises (a) Control of the diabetes but not so strictly that hypoglycemic reactions are likely (b) Eradication of infection This is done by gentle release of confined pus from which a culture is grown and the sensitivity of the pathogenic organism to penicillin, aureomycin, chloromycetin, terramycin, streptomycin and neomycin is determined This determination of the sensitivity of the organism we consider to be a highly important procedure, as it usually gives the clue to which antibiotic or combination of antibiotic agents can be expected to give the most benefit Between the time that the culture is taken and the report on the sensitivities is received we give procaine penicillin, 150,000 units, intramuscularly daily Thereafter, suitable doses of the appropriate antibiotic agent are given (c) Where crusts of dried exudates are present or without evidence of trichophyton infection the affected foot is soaked in a solution of potassium permanganate 1 8000, the temperature of which should not be lower than 90° F (32 2° C ) and not higher than 105° F (40 5° C) for one-half hour three times daily (d) Subsequent to the foregoing local treatments local applications of Furacin or tyrothricin have been valuable (e) Improvement of the arterial circulation in the limb may be accomplished by intermittent venous occlusion if there is no venous insufficiency Barring contraindications, as already noted, other methods may be tried (see p 190) The presence of an acute infection calls for complete rest of the affected part and as a result most of the measures that are of use prophylactically are to be avoided when infection is present (f) Ligation of femoral veins has yielded gratifying results in a few carefully selected cases in which pain was predominant and in which indolent gangrenous ulcers were at a standstill Occasionally the results from this simple procedure are so spectacular that we commend it for more frequent consideration than it generally receives

*Imputation* The incidence of amputations has decreased with the growth of sulfonamide and antibiotic therapy Furthermore, when amputation is decided upon removal of the foot at the transmetatarsal site is done with

less prospect of subsequent higher amputations than was formerly the case A careful appraisal of the circulation—methods of which are outlined on page 184, will aid greatly in coming to the proper conclusion concerning the need for amputation Consideration is also given to the fact that the occlusive vascular disease is not confined to the legs but that the vessels of the heart, brain and kidneys have not escaped Despite these considerations, with the skill of the surgeon, the advances in anesthesiology, and the newer drug therapies, these patients with widespread vascular disease do wonderfully well when subjected to surgery

The indications for amputation are

1 Extensive gangrene with no improvement under conservative treatment and in a limb which is extremely impoverished of circulation

2 Deep extensive and extending infection, and especially with an extensive osteomyelitis which is intractable to more conservative measures A phalanx may be safely removed if the osteomyelitis is limited to a phalangeal bone

3 Intractable pain with evidences of extreme grades of organic vascular occlusion—great care being taken not to be mistaken by a peripheral neuritis

SITE OF AMPUTATION The level at which the amputation will be done is decided upon after a careful appraisal of the local circulation The site selected should be high enough to be in a relatively well vascularized zone If in the process of removing a limb the surgeon finds more extensive occlusive disease and less bleeding than he thinks might promise good postoperative progress a higher site is immediately selected In general, it is wise, in case of doubt to select the higher of two contemplated sites Roentgen ray films may show a marked degree of arterial obstruction just above the knee The amputation in such a case would be above the obstruction unless the evidences of an efficient collateral circulation were marked

*Anesthetic* The choice of anesthetic is made by a competent anesthetist Generally, spinal anesthesia is used for amputations However, if there is an extreme degree of infection and necrosis and the patient shows marked evidences of a toxemia, the circulation of the limb is entirely obliterated by placing a tourniquet above the knee sufficiently tight to stop the arterial circulation, and the limb is refrigerated by packing it in ice to a point several inches above the tourniquet[14] After several days, with the pronounced clinical improvement that is usual, the leg is amputated above the level of the tourniquet With refrigeration no other anesthetic agent is used In properly selected cases we have found the foregoing procedure to be an excellent one Ordinarily the procedure of amputation causes little difficulty in maintaining control of the diabetes but when necessary the same measures are used as are employed with other surgical procedures as outlined on page 221

### V. *Renal Disorders and Diabetes*

Two renal disorders—*intercapillary glomerulosclerosis*, frequently referred to as Kimmelstiel Wilson's disease, and *pyelonephritis*—deserve special consideration because of the high incidence with which each is associated with diabetes. From the pathologist's point of view a third renal disorder—*glycogen nephrosis*—might be added. It is recognized only at autopsy by the presence of glycogen in the renal tubules and its presence bears a direct relationship to the lack of control of the hyperglycemia and glycosuria immediately preceding death. Glycogen nephrosis is of no known clinical significance except as a manifestation frequently associated with glycosuria.

**Intercapillary Glomerulosclerosis.** *The increasing incidence of intercapillary* glomerulosclerosis and the unfavorable prognosis it carries, when associated with diabetes, make this complication one of the most serious of the chronic complications. The disorder is not confined to diabetic patients but it is only in such patients that it occurs in an advanced form—doubtless because of the accelerating influence untreated diabetes exerts on the progress of degenerative disorders.

The association of intercapillary glomerulosclerosis with diabetes was recognized in 1936.[15] Its increasing incidence has been attributed to the increased longevity of diabetic patients. Time will probably show that other factors are at work and possibly some feature or features of present day therapy for diabetes will play a part.

Intercapillary glomerulosclerosis is identified by the presence of deposits of hyaline *masses in the central portions of the glomerular nodules* (Fig 9). Pathologists are not agreed about the source of the hyalin. An increasing number believe that the deposits are made in the capillary wall and not a sclerosis and hyalinization of the interstitial tissue as postulated by Kimmelstiel and Wilson. These changes have been observed in 18 to 63 per cent of diabetics *coming to autopsy.*[16] Lukens[1] *observed identical changes* in the kidney of a dog kept diabetic for five years, after injections of crude extract of anterior pituitary glands.

The clinical manifestations originally reported upon were diabetes, albuminuria and edema. We have observed patients who fulfilled these criteria and in whom the disease ran a benign chronic course for many years. *Albuminuria* is the first indication of this complication. It tends to be intermittent at first as does *edema*—the second manifestation of intercapillary glomerulosclerosis. The degrees of involvement and the progressive tendencies are variable. All graduations of this complication are seen from the initial mild form to the advanced and malignant stage with full develop*ment of the nephrotic manifestations and with a life* expectancy measured in months instead of years. In such cases we find *diabetes of long duration, retinal hemorrhages, edema of the extremities* (*or generalized*), *elevated*

*arterial blood pressure, albuminuria, hyaline casts and red blood cells in the urine, hypoproteinemia, mild to moderate degrees of anemia and varying degrees of renal insufficiency*

Intercapillary glomerulosclerosis occurs about twice as frequently in males as in females *It is most frequent in the third and fourth decades of life,* is rarely seen in the second decade, and the onset decreases in frequency in those over forty years of age In our patients having this complication, almost without exception, a history of poor control of the diabetes was secured This is what one might expect when it is realized that *no young diabetic escapes degenerative arterial disease if the diabetes is poorly controlled*

*Prevention and Treatment* Prophylactic and therapeutic measures are directed toward improving the patient's general clinical condition and are as follows 1 *Control of the diabetes* This is accomplished as indicated in Chapter XIII with the following modifications

2 *Diet If there is no elevation of the blood urea nitrogen values (above* 15 mg /100 cc ) a liberal *protein* intake—up to 140 gm daily—is allowed to compensate for the loss of protein in the urine and in the attempt to replenish depleted protein stores With urea retention the amount of protein is set at approximately 0 33 gm per pound of the standard body weight plus an amount approximately equal to that of the protein lost in the urine daily Liberal allowance of *carbohydrate,* 275 to 335 gm daily, will aid in sparing kidney function The total calories are calculated as for uncomplicated diabetes (p 105) This diet will permit a low fat content which is desirable in any complication of diabetes in which degenerative changes in the arteries are prominent The *restriction of the salt intake* to a mini*mum is highly desirable in the presence of edema but this restriction is* cautioned against as the edema disappears in those cases in which the blood urea value exceeds normal It is a simple matter to precipitate clinical uremia if this precaution is not heeded

*Hematinics* are worth a trial At best they are relatively ineffective and if the red blood cells are below 3 000 000 per cu mm a transfusion of whole blood, 500 cc, is given twice per week, until values closely approximating normal are reached

*Standard measures of coping with myocardial decompensation* are used when indicated *Diuretics* may be helpful but should be used cautiously if red blood cells are present in the urine in appreciable numbers

**Pyelonephritis.** *Pyelonephritis is a common and dangerous complication of diabetes* Diabetic patients, and especially diabetic women are predisposed to infections in the urinary tract Bowen and Kutzman[18] found normal urinary tracts in only 7 of 84 unselected diabetic women Pyelonephritis is four and *one half times more common* as a cause of death among diabetic than it is among nondiabetic patients,[19] and of 307 deaths of diabetic patients it was the sixth commonest cause Pyelonephritis was

the cause of 21 of these deaths[20] A peculiar form of pyelonephritis—a necrotizing renal papillitis—is associated mostly with diabetes A specific total necrosis of the renal pyramids occurs with, or without, abscess formation, and involvement of both kidneys is frequent This serious complication occurred in 25 per cent of the cases of acute pyelonephritis and accounted for the most severe forms of the disease "[1]

A sugar laden urine is probably a better medium for organisms than urine containing no sugar This feature and the higher frequency of bladder catheterization in diabetic subjects who have been in coma combine to increase the likelihood of pyelonephritis in these patients Also ptosis of the kidneys, particularly on the right side, which follows the rapid loss of weight, so common in these patients predisposes to kinking of the ureters and hence to infection These features are apt to play a part no matter how the infection reaches the kidney—whether it be by the hematogenous or retrograde routes or invasive extension from adjacent infections

Clinically, this complication in the typical case is characterized by the sudden onset of recurring attacks of fever, chills and backache The urine sediment contains pus and myriads of organisms, and albumin is present

The studies recommended in such a case comprise, first and most important, the identification of the organism by culture of the urine and the determination of its sensitivity to the various antibiotic agents Though the colon bacillus is the most common offender this is not an adequate reason for neglecting to determine, with certainty what organism, or organisms, are responsible Ten cases of infections of the urinary tract in which neomycin was the only antibiotic agent to which the infecting organism was sensitive illustrate the need for highly specialized selective study and therapy[21]

The predisposition of diabetic patients to tuberculous infections is well known The importance of identifying a renal tuberculosis while the infection is confined to one kidney is obvious

Second, the appraisal of physical abnormalities by a urologist this will comprise a phenolsulfonphthalein excretion test, a pyelogram—the dye being administered intravenously—and if found essential to establish the diagnosis a retrograde pyelogram is recommended

The treatment for pyelonephritis should be prompt and conservatively aggressive The diabetes is controlled as in the case of other acute infections (see p 213) The degree of glycosuria is reduced in some cases by sugar consuming organisms in the urinary tract This is a minor matter

The therapy against the infection will be dictated by the type of organism and to which of the remedial agents it is sensitive In the event sulfonamides are used as is frequently the case it is important that at least one specimen of urine per twenty four hours should be alkaline in reaction and at least 1500 cc of urine should be excreted in this period It is easier to secure one alkaline specimen by giving a single large dose of bicar

bonate of soda daily than it is to keep the urine alkaline by giving multiple smaller doses Gantrisin has gained popularity for its effect in sterilizing the urinary tract of gram negative organisms and the absence of renal complications attending its use

Surgical measures that are indicated should be carried out without fail if the patient s clinical condition permits The diabetes is not a deterrent to such corrective measures

VI *Ocular Lesions*

Ocular changes attributable to diabetes have a degenerative basis and as might be expected patients with degenerative ocular changes present a



*Fig 24 Diabetic retinitis Note the deep round hemorrhagic areas the waxy exudates* and decreased caliber of the arterioles

high incidence of arterial disease—hypertension and diseases of the coronary and peripheral arteries chronic renal disease and hypercholesterolemia *These ocular lesions have a definite and direct relationship to the duration of the diabetes*[60] and to its poor control Sixty per cent of patients having diabetes for more than ten years show retinal hemorrhages (Waite and Beetham) Poor control of the diabetes is not always evident, however, as some patients exhibit advanced degenerative changes and yet have a mild diabetes that has not been appreciably out of hand

The retinal abnormalities are the most frequent of the serious ocular complications They comprise

**A Vascular Changes** 1 Deep, rounded punctate hemorrhages—the

most distinctive diabetic earmark in the retina (Fig 24) They are venous in origin and are not necessarily related to arterial hypertension

2 Superficial hemorrhages which tend to be flame shaped They occur in the nerve fiber layer and are of arterial origin and are related to the degree of arterial hypertension and, in at least some cases, to capillary fragility

3 Engorgement of the retinal veins

4 Narrowing of the arterioles with evidences of sclerosis, and microaneurysms of the capillaries

B **Exudates** 1 Waxy exudates, which appear to be the result of hyalinization of the deep retinal hemorrhages

2 Cotton wool exudates

3 Lipid deposits

C **Proliferative Changes** *Retinitis Proliferans* In this abnormality there is a laying down of new tissues most probably in the attempt to correct previous damage As a result dense white areas of new tissue with newly formed blood vessels are to be seen and most frequently in the region of the macula Vision is impaired up to complete blindness depending on the areas involved Contraction of the scar tissue may cause separation of the retina Also, spontaneous hemorrhage may precipitate a hemorrhagic glaucoma

**Other Ocular Complications of Diabetes** These abnormalities do not assume the same degree of widespread clinical importance as retinitis does but are nevertheless, not infrequently encountered in diabetic patients

[illegible]

disorder

2 Corneal wrinkling demonstrable with a slit lamp and a corneal microscope

3 Transitory changes in refraction occurring for a short period after a hyperglycemia is corrected (see p 167)

4 Argyll Robertson pupil—this abnormality in nonsyphilitic diabetic subjects is a manifestation of neuropathic changes (see p 20[illegible])

5 Xanthelasma Patches of lipid deposits on the eyelids are an innocent complication of diabetes although they are not distinctive of this disease

6 Tobacco amblyopia has been observed by one of us in two diabetic patients recently Improvement followed the withdrawal of tobacco and the control of a mild diabetes in each instance

Treatment for ocular complications of diabetes includes

1 Control of the diabetes

2 The use of a diet liberal in protein not less than 100 gm for the male nor less than 90 gm for the female diabetic and including liberal amounts

of carbohydrate (250 to 335 gm ) and small amounts of fat—below 75 gm daily

3 Ascorbic acid, 200 mg daily, with rutin, 20 to 200 mg three times daily according to the degree of capillary fragility as determined by the Gothlin index test are worthy of a trial in cases of retinal hemorrhages

4 Cataracts are treated as in the nondiabetic subject

5 Transitory refractive errors due to a reduction of hyperglycemia are managed as outlined on page 167

6 Neurologic changes involving the eyes as part of a diabetic neuropathy are treated vigorously and in the same manner as other neurologic abnormalities (see p 207)

7 Xanthelasmic patches ordinarily should not be interfered with If removed they almost invariably recur

### VII *Neurologic Disturbances Complicating Diabetes*

Neurologic disturbances are among the most common complications of diabetes Collens and coworkers[73] found these abnormalities in 93 per cent of all their diabetic patients The cause or causes of these disorders are not entirely clear but accumulated evidences preponderantly indicate that disturbances in nutrition which accompany loss of weight in the presence of a long standing and poorly controlled diabetes are the usual precipitating factors Although uncontrolled diabetes and loss of weight are usual forerunners of these disturbances, this is not always so In fact, findings typical of the milder forms of so called diabetic neuropathy have been observed in patients before the diabetes developed Also, patients who have not lost weight and whose diabetes has been under excellent control for long periods may experience a mildly progressive neuropathy indistinguishable from that ordinarily accepted as diabetic in origin It would appear that there is an underlying disturbance which tends to be intensified by poor control of the diabetes and loss of weight but that these features are not essential to its development It is true however, that this type of neuropathy is seen for the most part but not exclusively in diabetic patients Acute infections and vitamin deficiencies may play a part but it appears that these, with the possible exception of vitamin $B_{12}$ deficiency, are modifying circumstances rather than essential features The neurologic abnormalities are degenerative in nature and it is not surprising that the other major degenerative disorders are frequently found in varying grades of development in subjects with neurologic disturbances We refer especially to diabetic retinitis, disease of the coronary arteries the kidneys and peripheral vascular disease The various neurologic disorders associated with diabetes are, in all likelihood, part of the same process but observed at different phases and under different circumstances they present features so variable that their separation into several categories is not surprising

The detection of a diabetic neuropathy in its early stages is of utmost

importance For this purpose studies of the vibratory sense are particularly valuable Disturbances in the vibration sense are recognized clinically by (a) decreased acuity or a complete inability to detect the vibrations of a tuning fork and (b) increased perception time Barach[24] and Collens[25] have attracted attention to the value of this examination We can support their claims and emphasize that the common error of attributing symptoms of neurologic origin to disturbances in circulation can be eliminated if proper investigation of each possibility is carried out We consider the neurologic survey to be one of the most *important* in appraising the clinical status of the diabetic patient

*For* the detection of an impaired vibration sense a tuning fork of an aluminum alloy with a frequency of 128 (Fig 25) serves admirably The detection of the vibration and the prompt recognition of its cessation—

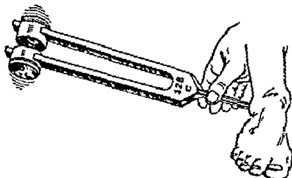



Fig 25 A tuning fork as used in the detection of disturbances of vibration sense

the patient's eyes being closed—is evidence of a normal vibratory sense The handle of the vibrating tuning fork is *applied* to bony prominences—the sternum, radius ulna crest of the ilium sacrum tibia, the malleoli and the metatarsophalangeal prominences—in determining the patient's vibration sense Studies involving upper extremities are done largely to acquaint the patient with the procedure Impaired vibration sense in the upper extremity occurs but not nearly as frequently nor to as great a degree as is observed in the legs and feet

*The degenerative* changes which account for the blocking of the transmission of the vibratory impulses occur in the posterior columns of the spinal cord and in the peripheral nerves In diabetes the latter is predominant

The vibration sense normally is less acute in older age groups, it is variable under normal circumstances and findings indistinguishable from those found in diabetes are observed in patients with tabes dorsalis and with primary or pernicious anemia

For practical purposes the following classification of the diabetic neuropathies has proved to be satisfactory

**Chronic Neuropathies.** A The *early* or *mild* and often ill defined form of diabetic neuropathy—the most common form—is gradual in onset and the symptoms, most frequently encountered and associated with loss of weight and uncontrolled diabetes for long periods, are vague pains aches, *shooting pains, cramps, numbness, tingling and burning, lightning stinging* or needling sensations, stiffness and formication, most frequently occurring in the legs and feet but occurring infrequently in the upper extremities and in the trunk *These symptoms tend to be worse at night and upon exposure to cold* The increasing intensity of these symptoms at night provides a clue in differentiating neurologic disturbances from a circulatory insufficiency Tendon reflexes are frequently impaired or absent Tenderness of the calf muscles is common and some impairment in the vibratory sense is *usual in the legs and feet in this relatively early phase*

This disorder may remain relatively stationary for long periods in some patients but characteristically it subsides readily with the control of the diabetes and with appropriate supplementary therapy

B The *moderately severe* stage of diabetic neuropathy is characterized by greater disturbances in the tendon reflexes, and in the vibratory sense The symptoms have been present for a prolonged period and areas of cutaneous paresthesia are often detectable We include also in this group those *cases with abnormalities of the autonomic nervous system which respond* satisfactorily to therapy in contrast to those which do not and which are classified in the severe or refractory group Falling in this moderately severe group are some cases of intermittent nocturnal diarrhea, or intermittent diarrhea and constipation, stubborn constipation of relatively recent onset, delayed emptying of the stomach, impotence, vasomotor instability causing giddiness on rising from the recumbent to the erect position due to orthostatic hypotension and absent sense of bladder filling These *patients tend to be underweight and indeed it is quite likely that malnutrition* plays a contributory part in the production and maintenance of this clinical state

*Involvement of the autonomic nervous system* is detected in patients having disturbances of the gastro intestinal and the genito urinary tracts The development of obstinate constipation or, as occurs in some instances, diarrhea which is especially troublesome at night, is not infrequent These two disorders sometimes alternate in a single patient The absence of free *hydrochloric acid from* the gastric secretions is a prevalent but not an essential finding Incontinence of feces has been noted Epigastric pain, indistinguishable from the gastric crises of tabes, is occasionally encountered Roentgenologic studies indicate disturbed *motility in the gastro intestinal* tract with, in some cases, a scattered barium pattern as seen in severe deficiency states Unlike the steatorrhea of pancreatic insufficiency, the diarrhea

of diabetic neuropathy is not influenced by the oral administration of pancreatic extracts

Involvement of the peripheral autonomic nerves leads to reduction or elimination of perspiration in the involved areas reduced vasomotor and pilomotor function and to dependent edema secondary to the altered permeability of the capillaries Reduced functioning of the sebaceous glands may account for the atrophic and shiny changes which the skin of the extremities undergoes

*Orthostatic hypotension* occasionally occurs as a result of neurocirculatory abnormalities in patients exhibiting characteristics of diabetic neuropathy Dizziness weakness on physical exertion and, in the more severe grades of the disorder, syncope occur in association with the decrease in blood pressure which follows the change from the supine to the standing position

*Disturbances in the genito urinary tract* identifiable with diabetic neuropathies include disturbances in sphincter control due to degenerative changes in the pudendal nerves permitting dribbling paralysis of the bladder with the "cord bladder syndrome—painless distention of the bladder with retention of urine, an impaired sense of bladder filling and a predisposition to infection in the genito-urinary tract Sexual impotence is a common complication This may exist with or without a loss of libido Loss of ejaculatory power may exist without loss of potentia but a combination of these disorders is the rule, with atony of the bladder an additional but less frequent complication

C. *The late, severe and relatively refractory neuropathies in the diabetic patient* are uncommon in contrast with the frequent occurrence of the milder forms The most frequent complaints when *peripheral nerves* are involved are loss of weight general weakness disturbed sensation in feet varying from numbness tingling pins and needles sensation, a feeling that "his feet do not belong to him," to complete loss of sensation with painless ulcerations Foot or wrist drop is an uncommon feature but unsteadiness of gait is not infrequent

Involvement of the peripheral nerves and the fasciculi proprii of the spinal cord causes disturbances in the tendon reflexes There may be complete absence of all reflexes but *diminished or absent Achilles reflexes* are especially frequent, as is a depression of the peripheral superficial sensibilities *Reduced pupillary responses* to light even to the degree observed in the Argyll Robertson pupil have been observed

Cases of *neurotropic feet* in which there is complete loss of sensation and great destruction of bone (Fig 26) are uncommon although we have seen five such cases in the past year Chronic ulcerations of the feet may be mistaken for diabetic gangrene on the basis of arteriosclerosis obliterans but in the cases we have seen the tips of the toes have been warm and there has been excellent pulsation of the peripheral arteries of the feet. Destruc-

tion of bone and the extrusion of bony fragments through a sinus at the base of an ulcer may occur Shortening and stubbiness of the foot develops as a result of marked destruction of bone

There are evidences that, in some cases, this destruction of bone is due to a secondary infectious process but in others the disorder appears to be on a purely neurotrophic basis

In cases of extreme degree irreparable organic changes in the nervous system have been noted The following case report is illustrative

J C a male pharmacist aged forty three years when admitted to the Pennsylvania Hospital in 1949, gave a history of having had diabetes mellitus for fourteen years During that period the diabetes was under irregular control, with 35 to 50 units of insulin daily

About two years previously there was swelling of the right foot At first this swelling disappeared on bed rest but later it became constant Four months before admission he experienced numbness of the feet and of the fingertips About the same time edema of the left foot and an ulcer on the right great toe appeared Later an ulcer appeared on the left great toe and another under the proximal end of the left metatarsal bones.

He gave no family history of diabetes He had had chronic intermittent diarrhea with "milky fatty stools" of three years' duration anemia with pallor, and dizziness of similar duration left abducens nerve weakness and diplopia for six weeks and morning nausea, relieved by food, of seven months' duration The patient's weight had been from 132 to 134 pounds (60 to 61 kg) for the preceding eight months

The physical examination revealed A systolic blood pressure of 178 mm Hg with a diastolic pressure of 120 mm, normal pupillary reactions to light, arteriovenous nicking of the retinal vessels arteriolarsclerosis round hemorrhages and waxy yellow exudates on ophthalmoscopy, generalized pallor of the skin and mucous membranes, the liver was not palpable, 4 plus pitting edema of the right foot, ankle and lower leg, 1 plus edema of the left foot and ankle, with a marked increase in ... lcer beneath the

absence of touch, pain, vibration and position sensation in the feet and ankles bilaterally, hypalgesia over the dorsolateral surface of both legs loss of vibration sense in the tips of all fingers of the right hand and in the fourth and fifth finger tips of the left hand, tenderness over the course of the femoral and peroneal nerves and absent patellar and Achilles tendon reflexes bilaterally, and a positive Romberg sign was elicited

... from 1010 to 1018 2 to 4 ... al ... lls ... n

serum albumin of 3.5 gm. and a cholesterol value of 310 mg Phenolsulfonphthalein excretion tests showed that 5 to 10 per cent of the dye was excreted in twenty minutes with a total two-hour excretion of 30 to 35 per cent There was a marked excess of fat in the stools Gastric secretion contained less than normal amounts of free hydrochloric acid prior to the administration of histamine Serologic tests on

... ed but incomplete destruction ... cts (Fig 26) There was considerable soft tissue swelling and periosteal proliferation along the lateral margins of the fourth and fifth metatarsal bones In the left foot only two indistinct radiolucent areas in the cuboid bone and periosteal proliferation along the fifth metatarsal

were observed. Films of the hands were negative except for areas of bone destruction at the distal end of the middle phalanx of each middle finger.

During the patient's course in the hospital, his diabetes was controlled by 42 units of protamine zinc insulin and 13 units of regular insulin given separately before breakfast and a 2800-calorie diet containing 175 gm. of protein, 300 gm. of carbohydrate and 100 gm. of fat in three equal feedings and a bedtime nourishment.

He was given transfusions of whole blood, dilute hydrochloric acid by mouth, a course of penicillin therapy, supplementary vitamins, and boric acid solution soaks and furacin ointment applied locally to the pedal ulcerations.

*The diarrhea promptly ceased and the stools became normal;* the hemoglobin concentration rose to 12 gm. per 100 cc. and the red cell count to 4.0 million per cu. mm. The blood urea nitrogen concentration remained elevated but was not made [illegible] sted. [illegible] 120 [illegible] ared [illegible] tures

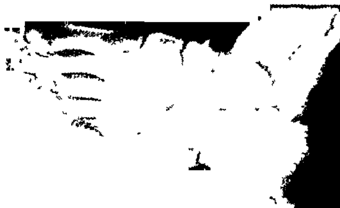


Fig. 26. Extensive destruction of bone as seen in a case of neurotrophic foot in a diabetic patient. ([illegible])

persisted. The ulcerations healed slowly and incompletely. There was no change in the neurologic abnormalities or in the appearance of the bones of the feet on roentgen ray films.

This patient had diabetes mellitus, diabetic retinopathy, neuropathy with neurotrophic ulcerations and bone lesions of the feet, and intercapillary glomerulosclerosis (Kimmelstiel-Wilson's disease).

Subsequent to discharge a prolonged course of vitamin $B_{12}$ therapy was without striking benefit, although after two years the degenerative disorders do not appear to have progressed unfavorably.

*Treatment for Diabetic Neuropathy.* Vitamin $B_{12}$ has been, in our experience, the most promptly effective measure in correcting these neuropathic disorders. It is given intramuscularly in doses of 30 micrograms daily for three to five days and thereafter once per week has been adequate. The relief from night pains and from the swaying or giddiness on walking has been so prompt as to leave no uncertainty about the specific relief which this drug provides. Also, a return of the vibratory sense is noted withi

few days and a more gradual correction of impotence has been observed Relief also follows the administration of large doses of vitamin B complex but it is achieved at a considerably slower rate

Control of the diabetes and especially if the diet is low in calories and unless fortified with vitamins may increase the intensity of the neurologic manifestations This is avoided by giving a diet of sufficiently high caloric value to prevent a reduction in weight for the time being, by controlling the diabetes with insulin and by employing vitamin $B_{12}$ therapy

**Acute Peripheral Neuritis** This distressing complication is infrequent in contrast to the common chronic neuropathies Sciatica serves to illustrate this group The onset of this true form of peripheral neuritis is usually rapid with severe pain throughout the distribution of the involved nerve, intensified by motion and with exquisite tenderness on pressure over the nerve, and with tender muscles Involvement of the muscular function varies from a mild degree of weakness to actual paralysis as seen in foot or wrist drop Atrophic changes occur in prolonged cases Absent tendon reflexes in the involved zones, e g, the Achilles reflex in cases of sciatica, is characteristic Poisoning with heavy metals, thiamine deficiency, infections, exposure to cold and pressure on or invasion of, nerve trunks by neoplastic growths, are causes of peripheral neuritis and are to be considered in addition to the diabetes When directly attributable to the disturbed physiology associated with diabetes the duration of attacks varies from three to twelve weeks

*Treatment* Therapy for acute peripheral neuritis in the diabetic is identical with that for the nondiabetic with the added features (a) *prompt control of the diabetes*, and (b) the prevention of a loss in weight The reduction of body weight tends to intensify the symptoms and great care should be taken to maintain the existing weight, even in the obese patient, until the neuritis is corrected

*Thiamine hydrochloride*, 50 mg, is administered intramuscularly daily until relief is secured, and vitamin $B_{12}$, 30 micrograms, is given intramuscularly daily for three to five days and thereafter once weekly

Other features of treatment are *rest in bed*, and infra red heat treatments over the involved areas for at least one half hour several times daily

*Acetylsalicylic acid*, 0 6 gm (10 gr ) three times during the day, and *an enteric-coated tablet of sodium salicylate*, 0 6 gm (10 gr ) before retiring are recommended When the pain is severe *codeine sulfate*, 0 03 gm (0 5 gr ), may be used to supplement the salicylates

### *VIII Tuberculosis*

Diabetic patients are especially susceptible to tuberculous infections Pulmonary tuberculosis was about twice as common in 3106 diabetics as in a comparable nondiabetic group[26] It was three times as common in those taking more than 40 units of insulin daily as in those taking less or

*no insulin, and tuberculosis was about twice as common in diabetic patients* who were below the standard weight in contrast with those above standard weight. Attacks of diabetic coma predispose to the development of pulmonary tuberculosis.

TABLE 31

THE SIMPLICITY OF THE CONTROL OF A SEVERE DIABETES DURING A FEBRILE PHASE OF AN ACTIVE PULMONARY TUBERCULOSIS

A B Weight 59 Kg Height 176 Cm

*Diagnoses* Diabetes Mellitus Active Pulmonary Tuberculosis

| DATE 1946 | BLOOD SUGAR (Mg.) | GLYCOSURIA AND ACETONURIA: 7 A.M. to 11 A.M. | 11 A.M. to 5 P.M. | 5 P.M. to 9 P.M. | 9 P.M. to 7 A.M. | INSULIN UNITS | DIET |
|---|---|---|---|---|---|---|---|
| Oct 10 | 308 | 4+ / 4+ | 4+ / 1+ | 4+ / [illegible] | 3+ / 0 | 50 P Z I, 24 Globin before breakfast | P 100, F 122, C 2[illegible]5, Cal [illegible]500 |
| 11 | | 4+ / 0 | 2+ / 0 | 4+ / [illegible] | 3+ / 0 | 65 P Z I, 24 Globin before breakfast | |
| 12 | 2[illegible]2 | | | | | 90 P Z I, 50 Globin before breakfast, 8 Crystalline before supper | |

Diet and insulin divided into four equal amounts and given at six hour intervals

| | | 3 A.M. to 9 A.M. | 9 A.M. to 3 P.M. | 3 P.M. to 9 P.M. | 9 P.M. to 3 A.M. | CRYSTALLINE INSULIN: 3 A.M. | 9 A.M. | 3 P.M. | 9 P.M. | DIET |
|---|---|---|---|---|---|---|---|---|---|---|
| 13 | | + / 0 | 4+ / 0 | 0 / + | + / 0 | 3[illegible] | 30 | 29 | 29 | P 100, F 12[illegible], C 2[illegible]5, Cal [illegible]300 |
| 14 | | 0 / 0 | 0 / 0 | 0 / 0 | 0 / 0 | [illegible]0 | [illegible]0 | 24 | 23 | |
| 15 | | 0 / 0 | + / 0 | 0 / 0 | 0 / 0 | 24 | [illegible]4 | 21 | [illegible]1 | |
| 16 | | 0 / 0 | 2+ / 0 | 0 / 0 | 0 / 0 | 25 | 24 | [illegible]5 | [illegible]1 | |
| 17 | | — | | 0 + | 0 / 0 | 24 | 21 | 23 | [illegible]4 | |
| 18 | | | 0 / 0 | 4+ / + | 0 / 0 | 24 | [illegible]4 | [illegible]4 | 24 | |
| 19 | | 0 / 0 | 0 / 0 | 0 / 0 | 0 / 0 | [illegible]4 | 24 | 20 | 20 | |
| 20 | | 0 / 0 | 0 / 0 | 0 / 0 | 0 / 0 | [illegible] | [illegible] | [illegible] | [illegible] | |
| 21 | 139 | 0 / 0 | 0 / 0 | 0 / 0 | 0 / 0 | 29 | 20 | 29 | [illegible]9 | |

Note Underscored figures represent results of tests for acetone P Z I = Protamine zinc

*Prevention* Patients are cautioned against contact with individuals known to have tuberculosis. It is highly desirable for every diabetic, and especially if he is underweight, to have a roentgen ray film of his chest once yearly. Good hygienic measures aid in preventing tuberculous infections.

*Treatment* In general, the treatment for tuberculous infection in the diabetic is the same as in nondiabetic The diet is sufficiently liberal to prevent a reduction in weight during acute episodes of the disease and at no time should the tuberculous diabetic be permitted to reduce his weight below the normal standard (see Appendix p 266) *It is preferable to keep* the body weight 5 to 10 per cent above this standard

Tuberculous infections may not alter the need for insulin greatly Additions to the usual insulin frequently suffice to control the diabetes but in some, especially those with secondary infections, it is necessary to employ the four equal meal schedule—a meal every six hours with an appropriate amount of insulin before each (see p 215) It is highly important that the diabetes be continuously controlled Repeatedly we have observed patients do badly at times when the diabetes was out of hand Occasionally, as the tuberculous process progresses the need for insulin becomes less It is not true that tuberculous patients derive benefit from a hyperglycemia

*The prompt control of the diabetes in the case of A B is depicted in* Table 31 It was not until this favorable progress was made that there was the slightest sign of his tuberculous infection abating

[illegible]

[illegible] Chapter XVI and illustrated in Table 31 [illegible] increasing the [illegible] of crystalline [illegible] On October 13 and thereafter the diet was equally divided and given at six hour intervals Note how promptly the correct amounts of insulin were determined and also that the total amount was reduced by October 20 to 80 units This satisfactory control was readily accomplished without any apparent abatement in the febrile course of the underlying disorder However the ensuing clinical improvement was prompt This is not a singular result

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CHAPTER XVI

# Acute Complications of Diabetes

Diabetic patients are exposed to the same *acute complications as non diabetics* but there are certain abnormalities to which they have a special predilection (see Table 32) Of the latter, *diabetic coma* (discussed in Chap XVII), *myocardial infarction* and *acute infections* complicating occlusive vascular disease in the extremities are the most common Infectious processes are among the most common acute complications of diabetes and it is not an unimportant fact that in most instances these acute episodes are superimposed on chronic degenerative disorders, notably arterial disease *This circumstance* tends to modify the treatment as well as the prognosis Myocardial infarction is an acute and serious complication which occurs, in a large part, as the result of chronic degenerative changes in the coronary arteries The clinical aspects of chronic and acute coronary artery

TABLE 32

THE RELATIVE INCIDENCE OF ACUTE COMPLICATIONS IN 514 CONSECUTIVE DIABETIC PATIENTS ADMITTED TO THE PUBLIC WARDS OF THE PENNSYLVANIA HOSPITAL

| | |
|---|---|
| Skin Infections | 67 |
| Respiratory Tract Infections | 65 |
| Urinary Tract Infections | 56 |
| Cardiac Failure | 46 |
| Gangrene of Lower Extremity | 43 |
| Myocardial Infarction | 38 |
| Gynecologic Conditions | 33 |
| Fractures | 28 |
| Cerebral Vascular Disease | 21 |
| Diabetic Ketosis | 14 |
| Cancer of Digestive Tract | 12 |
| Peritonitis | 8 |
| Cholecystitis | 8 |
| Osteomyelitis | 6 |
| Cancer of Respiratory Tract | 6 |
| Embolism | 6 |
| Hyperthyroidism | 5 |
| Miscellaneous | 171 |
| Total | 633 |

insufficiency including coronary occlusion, and the myocardial infarction which results, are dealt with on page 181.

## ACUTE INFECTIONS

Acute infections are the most common of the acute complications. They impair the effectiveness of insulin and tend to precipitate a high degree of hyperglycemia and diabetic ketosis progressing to coma with great speed, that is, in a matter of hours. The effect of fever alone, and fever plus infection on the duration and degree of the blood sugar lowering effect of insulin in contrast with the effect when no fever nor infection nor leukocytosis are present is diagrammatically depicted in Figure 27. For these

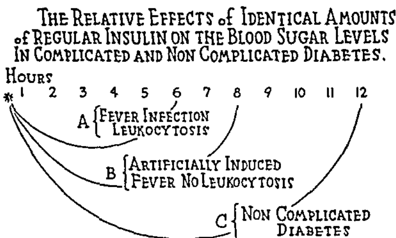



Fig 27 The differences in the blood sugar lowering effect and the duration of the effectiveness of identical doses of regular insulin under normal and abnormal circumstances are diagrammatically presented (Duncan, Carey and Hudson, Medical Clinics of N A, Nov 1939)

reasons and the fact that recovery from infections is retarded if the diabetes is not adequately controlled, special attention toward the prevention of infection and a special alertness when infection is already present yield high clinical dividends.

Diabetes is more difficult to control during acute infections and it is for this reason that changes in the distribution of the diet and insulin are usually made—changes which permit more certain and prompt control of a diabetes which under the abiding circumstances is likely to get out of hand with remarkable rapidity.

Patients with uncontrolled diabetes have a subnormal resistance to infectious organisms, especially to the tubercle bacillus and the *Staphylococcus aureus*.

All of the reasons why acute infections affect the diabetes so unfavor

ably are not known but we do know that infections which increase the need for insulin most markedly are those causing *fever* and *leukocytosis*, and that the behavior of the diabetes is *frequently a reliable index*, *favorable* or unfavorable, of the trend of an infectious process The duration of insulin action is reduced as is its degree of action by acute infections accompanied by fever and leukocytosis Infections not causing fever have little effect on the insulin need and those which cause no leukocytosis cause relatively little increase in the need for insulin Viral infections and tuberculosis are examples of the latter If secondary pyogenic organisms get a foothold, as in the case of an acute sinusitis complicating a simple coryza of viral origin or a mixed infection in a case of pulmonary tuberculosis, a change in the need for insulin is likely to be prompt

Increases in tissue metabolism, derangement of enzymatic processes and increased proteolytic activities in the blood in patients having a fever and leukocytosis may explain the behavior of the need for insulin but, until *the problem is clearer and until more specific means of attacking it are* available, we are obliged to continue with the excellent therapeutic means at hand, even if they may appear cumbersome

It will be concluded from the foregoing remarks that patients who have mild diabetes and ordinarily not needing insulin will almost always require insulin if an acute infection is contracted There are a few patients who have no detectable evidences of diabetes under normal circumstances but who have manifest diabetes during the course of an acute infection, notably infections due to the *Staphylococcus aureus* and especially carbuncles

**Prevention** Preventive measures comprise immunization when practicable control of the diabetes an adequate diet, hygienic care of the skin and special care of the feet, as has been stressed already

**Treatment for Acute Infections** *General Considerations* The features in therapy for diabetic patients suffering from acute infections are

A Cognizance of the effect which infections exert on the diabetes and *on the need for insulin*

B Specific measures directed toward eradicating the infection—drainage, antibiotic or sulfa therapy, and the occasional use of antitoxin

C Insulin therapy—who should receive insulin, the brand of insulin, the amounts and the distribution

*D Diet therapy—alterations in diet and in its distribution*

E Special measures—surgery, roentgen ray irradiation intravenous therapies

*Specific Considerations* A The effect which infections exert on the diabetes has been discussed at the outset of this section, page 213

B Specific measures *to be taken to eradicate infection* are of great importance The high degree of specificity with which antibiotic drugs overcome bacterial infection makes the early identification of the offending

organism or organisms and their respective sensitivities to the various antibiotic agents of great importance *Best results will follow if material for a culture is secured at once before any antibiotic agent is given* The material for culture growth may be from a carbuncle, furuncle, abscess, discharging sinus, an ulcer, the urine, the blood, the spinal fluid, etc

This procedure need not delay therapy As soon as the culture material is secured the antibiotic agent which seems most likely to be effective is given Too often we find carbuncles which have been doing badly and threatening life, only to find that the offending organism is resistant to the antibiotic—practically always penicillin—that the patient has been receiving The broader is the scope of the bacteriology laboratory in detecting the specific sensitivities the more often prompt cures will result

Other specific measures should not be overlooked, e g, adequate drainage in cases of pent up purulent material

INSULIN THERAPY Insulin is given to every patient, no matter what is the degree of severity of his diabetes, if his fasting blood sugar level exceeds 120 mg per 100 cc or if the postprandial value exceeds 160 mg per 100 cc

We use regular insulin exclusively during the course of moderately severe and severe infections In many cases, however, the disturbance is so slight that small to moderate increases in the amount of long acting insulin given will suffice without disturbing the usual routine For the more severe infections regular insulin only is used It is not used in combination with a slowly acting insulin because the latter does not exert a uniform effect throughout the twenty four hours

The action of regular insulin is prompt and the fact that its action is of short duration makes it a simple weapon to manipulate when both the blood sugar level and the insulin requirement may be subject to rapid alterations

The following method of distributing the insulin has been employed at the Pennsylvania Hospital for the past seventeen years with favorable results During the course of moderately severe infections the insulin is given in four divided doses at evenly spaced intervals The diet is similarly divided so that the patient receives the same amount of carbohydrate fat and protein after each injection of insulin It is convenient to give meals and insulin at 6 A M, 12 noon, 6 P M and 12 midnight This program permits the uniform control of the blood sugar level during the most severe complications Changes in the dosage of insulin are regulated according to the amount of sugar found in the urine, which is collected before each nourishment and by the level of the blood sugar (see Table 33)

Occasionally, in cases of very severe infections and in which very large amounts of insulin several hundreds of units daily, are given, it has been a temporary expedient to divide the insulin into six doses and the diet into

six equal nourishments, both given at four hour intervals As the critical phase passes, the injection of insulin and a nourishment are given every six hours

*The regulation of the insulin dosage in the case of a patient taking 80 units of insulin prior to admission for treatment for a carbuncle* is illustrated in Table 33

In the unusual case when meals and insulin are given at four hour intervals, collections of urine are made for the same periods, and likewise when meals and insulin are given every six hours, the urine is collected each six hour period The bladder is emptied before each feeding and the degree of glycosuria is determined

The degree of, or the absence of, glycosuria is a suitable guide in changing the dosage of insulin (see Table 33), but occasional blood sugar determinations are of value *Of great value is the testing of the plasma for acetone* The patient is in no danger from ketosis if there is no detectable acetone in the plasma or serum For the technic of performing this test, see

TABLE 33

AN ILLUSTRATIVE GUIDE TO INSULIN THERAPY IN THE CASE OF AN ACUTE INFECTION

| *Time* | *12 M* | *6 P M* | *12 M* | *6 A M* | *12 M* | *6 P M* | *12 M* | *6 A M* | *12 M* |
|---|---|---|---|---|---|---|---|---|---|
| Glycosuria | 4+ | 4+ | 3+ | 2+ | 0 | 1+ | 0 | 0 | 0 |
| Acetonuria | 2+ | 1+ | 1+ | 0 | 0 | 0 | 0 | 0 | 0 |
| Plasma Acetone | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Blood Sugar mg /% | 320 | | | | | | | 135 | |
| Insulin | 25 | 40 | 50 | 40 | 35 | 35 | 30 | 25 | 25 |

page 69 If the patient's condition is not progressing favorably and the infection is of a serious nature and there is acetone in the urine, a test for acetone in the plasma is advisable at least twice daily The presence or absence of acetone in the urine ordinarily is a good guide but if the reaction is 4 plus it is important to know to what extent the acetone bodies are *accumulating in the blood*

The change from the pre-complication insulin regimen is illustrated in Table 34 *This program is illustrative only* It provides a simple means of crudely estimating a safe initial program of insulin therapy, following which the amounts of insulin given are altered as indicated according to the degree of, or absence of, glycosuria as illustrated in Table 34 The initial dose of insulin for the patient having a mild diabetes can safely be 12 units For those receiving insulin routinely the initial dose will not be excessive if it equals one quarter of the routine dose plus a moderate increase *The determination of the initial dose is illustrated for varying de-*

grees of insulin need, in Table 31 The insulin is increased at each injection until the diabetes is brought under relatively good control It is well to maintain a fairly firm rein on the diabetes To do this when the time to reduce the insulin dosage arrives it is preferable to reduce and *not to omit* a dose Nothing will upset diabetic control more quickly than omitting a dose of insulin when a reduction in the amount given is all that is needed As the infection subsides the insulin is reduced steadily to prevent hypoglycemic reactions The need for great reductions is often necessary following the prompt correction of an infection In such cases there is little danger in making big reductions—as long as heavy reactions for glycosuria are not present—until the pre-complication dosage of insulin is nearly approximated

The pre-complication regimen is resumed after one or two days have elapsed without fever This can be done abruptly, e g, 20 units of regular

TABLE 31

A GUIDE IN CHANGING THE RESPECTIVE INSULIN PROGRAMS IN THE EVENT OF ACUTE COMPLICATIONS

| PRIOR TO COMPLICATION | DURING COMPLICATION—THE INITIAL DOSE—REGULAR INSULIN |
|---|---|
| (1) No insulin | 12 |
| (2) Single doses of 30 units or less of P Z insulin Globin or NPH insulin | 15 |
| (3) Combined insulin therapies totaling 80 units | 25 |
| (4) Combined insulin therapies—total 100 units | 40 |
| (5) Combined insulin therapies—total 130 units | 50 |

Note The initial dose is one-quarter of the former daily dose *plus* a moderate increase Subsequent doses will be adjusted according to the degree of glycosuria in each succeeding six-hour urine fraction

insulin given at six hour intervals (total for twenty four hours—80 units) is replaced by 60 units of protamine zinc insulin and 20 units of regular insulin injected separately

DIET THERAPY As has been indicated in the foregoing paragraphs, the diet is divided into four equal feedings during acute illnesses—except in rare cases when six equal feedings, one every four hours—are given

The diet requires some modification from the usual form It is important to maintain an adequate protein allowance—a minimum of 0.5 gm per pound of the normal body weight Liquids fortified with concentrated protein foods are desirable if the usual protein foods are unpalatable. Convalescence is speeded by giving more liberal allowances of protein—up to 0 66 gm per pound of body weight This protein quota is especially desirable in dealing with prolonged infections or open wounds such as ulcers from which much protein is lost Liquid nourishment may be all that the acutely ill patient can take and this should consist largely of fruit juices, skimmed milk, cream, gruels and ginger ale with glucose

### Diet XII
### Liquid Diet—Four Equal Meals
(Protein 110 gm, Fat 65 gm Carb 250 gm—2000 Calories)

| No Exchanges | Food Exchange | List No | Sample Menu | Household Meas | Wt Gm | P | F | C | Cal |
|---|---|---|---|---|---|---|---|---|---|
| 6 00 A M | | | | | | | | | |
| 1 | Bread | 4 | Oatmeal in | ½ c | 20 | 2 | — | 15 | 68 |
| 1 | Milk | 1 | Milk whole | 1 c | 240 | 8 | 10 | 12 | 170 |
| | | | Lactose or sugar or dexin | 2 tbsp | 20 | — | — | 20 | 80 |
| 2 | Meat | 5 | Eggs coddled | 2 | — | 14 | 10 | — | 146 |
| 1½ | Fruit | 3 | Pineapple juice | ½ c | 120 | — | — | 15 | 60 |
| | | | | Total | | 24 | 20 | 62 | 524 |
| 12 00 NOON (Repeat at 6 00 P M with suitable exchanges) | | | | | | | | | |
| | | | Soup (thin with broth) | | | | | | |
| 2 | Meat | 5 | Meat puree | 2 oz | 60 | 14 | 6 | — | 110 |
| 1 | Bread | 4 | Potato mashed | ½ c. | 100 | 2 | — | 15 | 68 |
| 1 | Vegetable | 2B | Peas puree | ½ c | 100 | 2 | — | 7 | 36 |
| 1½ | Fruit | 3 | Grapefruit juice | ¾ c | 150 | — | — | 15 | 60 |
| 1 | Milk | 1 | Milk whole | 1 c | 240 | 8 | 10 | 12 | 170 |
| | | | Lactose or sugar or dexin | 4 tsp | 15 | — | — | 15 | 60 |
| | | | | Total | | 26 | 16 | 64 | 504 |
| 12 00 MIDNIGHT | | | | | | | | | |
| | | | Milk drink | | | | | | |
| 2⅔ | Milk | 1 | Milk, skim | 1 pt | 480 | 16 | — | 24 | 160 |
| | Milk | 1 | Milk, skim powder | 1 tbsp | 12 | 2 | — | 4 | 24 |
| 2 | Meat | 5 | Eggs | 2 | — | 14 | 10 | — | 146 |
| | | | Lactose or sugar or dexin | 1 tbsp | 10 | — | — | 10 | 40 |
| 1 | Fat | 6 | Light cream | 2 tbsp | 30 | — | 5 | — | 45 |
| 2 | Fruit | 3 | Grape juice | ½ c | 120 | — | — | 20 | 80 |
| | | | | Total | | 32 | 15 | 58 | 495 |
| | | | | Day's Total | | 108 | 67 | 248 | 2027 |

This liquid diet is designed for patients with acute complications and who are unable to eat regular food The division into four equal meals, one every six hours in conjunction with four doses of regular insulin facilitates the control of the diabetes during emergency periods (see p 217)

DIET XIII
HOUSE DIET  FOUR EQUAL MEALS
(Protein 110 gm  Fat 65 gm  Carb 250 gm —2000 Calories)

| NO EXCHANGES | FOOD EXCHANGE | LIST NO | SAMPLE MENU | HOUSEHOLD MEAS | WT GM | P | F | C | CAL |
|---|---|---|---|---|---|---|---|---|---|
| 6:00 A M | | | | | | | | | |
| 2 | Bread | 4 | Bread | 1 sl | 25 | 2 | — | 15 | 68 |
| | | | Oatmeal | ½ c | 100 | 2 | — | 15 | 68 |
| 2 | Meat | 5 | Eggs | 2 | | 14 | 10 | — | 146 |
| 1½ | Milk | 1 | Milk skim | 1 c | 240 | 8 | - | 12 | 80 |
| | | 1 | Milk skim powder | 1 tbsp | 12 | 2 | — | 4 | 24 |
| 1 | Fat | 6 | Butter | 1 tsp | 5 | | 5 | — | 45 |
| 1½ | Fruit | 3 | Banana | ½ sm | 75 | | | 15 | 60 |
| | | | | Total | | 28 | 15 | 61 | 491 |
| 12:00 NOON (Repeat at 6:00 P M with suitable exchanges) | | | | | | | | | |
| 2 | Meat | 5 | Beef roast lean | 2 oz | 60 | 14 | 6 | — | 110 |
| 2 | Bread | 4 | Bread | 1 sl | 25 | 2 | | 15 | 68 |
| | | | Lima beans | ½ c | 90 | 2 | | 15 | 68 |
| 1 | Vegetable | 2A | Lettuce and tomato | 1 serv | 100 | | | | - |
| 1 | Vegetable | 2B | Carrots | ½ c | 100 | 2 | - | 7 | 36 |
| 1 | Milk | 1 | Milk skim | 1 c | 240 | 8 | — | 12 | 80 |
| 2 | Fat | 6 | Butter | 2 tsp | 10 | | 10 | — | 90 |
| 1½ | Fruit | 3 | Pear | 1 med | 150 | | - | 15 | 60 |
| | | | | Total | | 28 | 16 | 64 | 512 |
| 12:00 MIDNIGHT | | | | | | | | | |
| 1½ | Milk | 1 | Milk skim | 1 c | 240 | 8 | - | 12 | 80 |
| | | | Milk, skim powder | 1 tbsp | 12 | 2 | — | 4 | 24 |
| 2 | Meat | 5 | Cottage cheese | ½ c | 90 | 14 | 10 | — | 146 |
| 1 | Bread | 4 | Saltines | 5 | 20 | 2 | — | 15 | 68 |
| 1 | Fat | 6 | Butter | 1 tsp | 5 | — | 5 | — | 45 |
| 3 | Fruit | 3 | Grape juice | ¾ c | 180 | - | — | 30 | 120 |
| | | | | Total | | 26 | 15 | 61 | 483 |
| | | | | Day's Total | | 110 | 62 | 250 | 1998 |

This diet, equally divided into four nourishments illustrates that employed for treatment during acute complications when a dose of regular insulin is given at six hour intervals (see p 217)

A sample diet prescription is as follows

| | |
|---|---|
| Protein | 110 gm |
| Carbohydrate | 250 gm. |
| Fat | 50 gm |
| Total calories | 2000 |

This diet is presented in menu form as a liquid diet (Diet XII) and a diet of normal foods (Diet XIII) In each instance the diet is divided into four equal meals suitable for use in most cases of acute complications *Following the recovery from the acute complication the pre complication* diet is resumed simultaneously with resumption of the former plan of insulin therapy

PARENTERAL NOURISHMENT When a patient cannot take feedings by mouth or by gavage, an intravenous program of feeding is used being patterned on the six hour schedule outlined above *No method in present* use can supply adequate nutrition by this route, and caution must be exercised to use it no longer than necessity dictates and to prevent the excessive administration of sodium chloride

We have found the basic formula, for parenteral feedings as recommended by the National Research Council to be eminently satisfactory

To meet the requirements for the nutrition of a patient who will be unable to take any food or fluids for some days and therefore should receive a nutrient whicl will provide an adequate amount of some protein substitute.

| | |
|---|---|
| Water | 3 000 cc |
| Casein hydrolysate | 100 Gm. |
| Glucose | 200 Gm |
| Salt | 10 Gm. |

*This will require two liters of five per cent casein hydrolysate five per cent glucose* solution and one liter of 10 per cent glucose solution a total of 3 000 cc Since the casein hydrolysate is neutralized it will contain 5 Gm. of salt per liter or 10 Gm in two liters Other convenient formulae can be devised by which the volume can be kept below 3 000 cc [2]

An intravenous infusion of 750 cc is started every six hours and regular insulin is injected subcutaneously as each infusion is begun

The quantity of fluids given is adjusted to promote and maintain normal hydration Mild degrees of glycosuria are permitted as a safeguard against a hypoglycemia but sufficient amounts of insulin and carbohydrate are given to prevent appreciable degrees of acetonuria Blood sugar values are likely to be *misleading while glucose is being administered by vein*

The dosage of insulin is regulated in such cases also according to the degree of glycosuria For an unconscious or incontinent patient an indwelling catheter is introduced into the bladder, under appropriate *precautions* in order that the samples of urine may be secured Gantrisin is employed

in doses of 1 gm four times daily, as a prophylactic agent against infection in the urinary tract while the catheter is in place

The methods of therapy for diabetic patients having acute complications and surgery at the Pennsylvania Hospital have been reported and evaluated in some detail by Alexander, Loomis and Lee.[2] Considerable portions of the article which deal with surgery and diabetes are presented verbatim with the authors' consent

## SURGERY AND DIABETES

Insulin therapy has made it possible to give diabetic patients all of the benefits of surgery with prospects of results closely approaching those achieved with nondiabetic subjects For the relative frequency of surgical conditions in the acute complications see Table 35

TABLE 35

THE RELATIVE INCIDENCE OF SURGICAL COMPLICATIONS IN 511 CONSECUTIVE DIABETIC PATIENTS ADMITTED TO THE PUBLIC WARDS OF THE PENNSYLVANIA HOSPITAL BECAUSE OF ACUTE COMPLICATIONS

| | |
|---|---|
| Amputation of Extremity | 41 |
| Gynecologic Operations | 33 |
| Ligation of Vein | 32 |
| Intra-abdominal Surgery | 29 |
| Incision and Drainage | 21 |
| Sympathectomy | 15 |
| Operations on the Eyes | 10 |
| Normal Delivery of Child | 8 |
| Radical Mastectomy | 4 |
| Intrathoracic Operations | 3 |
| Thyroidectomy | 3 |
| Miscellaneous | 73 |
| Total | 275 |

The diabetes is controlled prior to elective operations but in emergencies diabetes is not a contraindication to surgical procedures provided a moderate or severe degree of ketosis is not present, i e., a 2 plus or greater reaction for acetone in the plasma or a $CO_2$ combining power of the plasma below 35 volumes per cent

**Procedure of Therapy** Our procedure in preparing these patients for operation has been as follows

1 *Elective Surgery* Patients undergoing elective surgery are kept on their usual routine of therapy until the day of operation

2 *Non-elective, Non-emergency Surgery* In non-elective surgery when a delay of two or three days is permissible, the diabetes is controlled using the four equal meals, one every six hours, and each preceded by a dose of regular insulin This is identical with the plan of therapy for acute infections (see p 217)

3 *Emergency Surgery* When immediate surgery is necessary and (a) the diabetes is not complicated by ketosis, no delay is indicated, but (b) when the patient has ketosis with a 2 to 3 plus reaction for acetone in the plasma or a $CO_2$ combining power below 35 volumes per cent, a delay of four to six hours will be adequate, with liberal doses of insulin given subcutaneously and glucose and normal saline given intravenously, to restore the carbohydrate metabolism and water balance sufficiently to proceed with the operation (c) Patients in diabetic coma should not be subjected to surgery beyond minor remedial measures, e g, myringotomy for the drainage of an abscess, the opening of an airway, the arrest of hemorrhage, or *other measures to forestall an immediate disaster*

*The Day of Operation* Procedures for this day are modified by the urgency and nature of the operation, the severity of the diabetes, the clinical condition of the patient, the anesthesia, the necessity in some cases for an empty stomach, and the prospective ability of the patient to take food orally after the operation

In dealing with the diabetes there are two main objectives (1) Avoid ketosis, and (2) avoid hypoglycemic reactions

Management of the diabetes is integrated with the other needs of the patient as indicated by our usual program, which is as follows

1 *Nourishment, Fluids and Sodium Chloride* The six hour schedule of *giving nourishment is adhered to The nourishment before operation is* given as 1 liter of 5 or 10 per cent solution of glucose Following operation the basic plan is to give 750 cc of a 5 or 10 per cent solution of glucose intravenously, slowly, in each six hour period A new bottle is started every six hours Every third bottle (or 1000 cc as the case may be) should be given as a 5 per cent solution of glucose in normal saline If nourishment is given in this manner for more than one or two days, casein hydrolysate is added—the equivalent of 25 gm of protein per day

On some occasions more fluids are indicated, in which case 1 liter is given in place of a 750 cc administration (see Fig 29) Contrariwise, in cases of surgical shock with anuria and a lower nephron nephrosis resulting, the amount of fluid would be reduced to approximately 1200 cc daily until urine is secreted We have had no occasion to resort to this measure for a diabetic patient

2 *Insulin Ordinarily one-quarter of the previous day's total dose of* insulin is given prior to the preoperative administration of glucose This is not a fixed rule It may be advisable to give less if there is any fear of hypoglycemia, if the operation is prolonged the risk of a hypoglycemia can be eliminated by giving glucose intravenously during the latter stages of the operation

Postoperatively the amounts of insulin, a dose every six hours, are regulated according to the degree of glycosuria Mild degrees of glycosuria are preferable during the first two or three postoperative days

Simple operative procedures—the ligation of veins, incisions and drainage, and dental extractions—and, indeed, many amputations may be performed without any change in the four meal schedule, the operation being simply inserted between feedings

Four illustrative plans of therapy in operative cases are presented in Figure 28 It will be observed that nourishments are given at 9 A.M , 3 P M.,

DIAGRAMS to ILLUSTRATE PLANS for MANAGEMENT of DIABETES on OPERATIVE DAY

For Incision and Drainage Vein Ligation and Similar "Minor" Procedures

3AM 6AM 9AM 12N 3PM 6PM 9PM 12M

FEEDINGS
IV GLUCOSE
INSULIN
OPERATION

For Amputation Setting of Fractures

3AM 6AM 9AM 12N 3PM 6PM 9PM 12M

FEEDINGS — LIQUID
IV GLUCOSE
INSULIN — REDUCED DOSE
OPERATION

For Amputation Transurethral Prostatectomy

3AM 6AM 9AM 12N 3PM 6PM 9PM 12M

FEEDINGS
IV GLUCOSE
INSULIN
OPERATION

GASTRECTOMY and THYROIDECTOMY and CHOLECYSTECTOMY

3AM 6AM 9AM 12N 3PM 6PM 9PM 12M

FEEDINGS
IV GLUCOSE
INSULIN
OPERATION

Fig 28. Four plans of therapy for diabetic patients subjected to surgery of varying degrees of complexity are depicted diagrammatically (After Alexander J B., Loomis, A H and Lee C. T., Jr Medical Clinics of North America Sept., 1949)

9 P M and 3 A M This timing is a matter of convenience and it obviously is quite as suitable if a 12 noon, 6 P M , 12 midnight, and 6 A M schedule is selected

The normal distribution of meals—usually three meals and a bedtime nourishment—and insulin are resumed when the patient is afebrile and can take regular food The transition from the six hour schedule to the normal

regimen is performed in the same manner as that following an acute infection (see p 217).

An illustrative operative case reported by Alexander and his co workers[2] is presented as follows:

A fifty eight year-old diabetic Negress, E P, was admitted on February 26, 1948 with a body temperature of 101° F and symptoms and signs which strongly suggested a diagnosis of acute cholecystitis Operation was deferred until the acute process had subsided

A cholecystectomy was performed on March 9, 1948, under nitrous oxide-oxygen ether anesthesia The pathologist's diagnosis was chronic cholecystitis and cholelithiasis A Wangensteen drainage was maintained for twenty four hours after operation Fever was present for three days postoperatively with a maximum of 101 2° F but convalescence was otherwise uneventful and the patient was discharged March 20, 1948, on the eleventh postoperative day

The diabetes was treated on admission by means of a 2100 calorie liquid diet divided into four equal feedings with 14 units of regular insulin before each feeding Prior to this illness the insulin requirement was 28 units a day Glycosuria was eliminated by the second day in the hospital On the day of operation, as shown in

| | 3/9/48 3AM | 9AM | 3PM | 9PM | 3/10/48 3AM | 9AM | 3PM | 9PM | 3/11/48 3AM |
|---|---|---|---|---|---|---|---|---|---|
| ORAL FEEDINGS | | | | | | | | | |
| IV GLUCOSE SOL | | | | | | | | | |
| INSULIN | | | | | | | | | |
| URINE SUGAR | 0 | 0 | 3+ | 2+ | 1+ | 1+ | 1+ | 0 | 0 |
| OPERATION | | | | | | | | | |

DIAGRAMMATIC REPRESENTATION OF ILLUSTRATIVE OPERATIVE CASE (CHOLECYSTECTOMY)

Fig 29 The plan of medical therapy for a diabetic patient (E P) undergoing a cholecystectomy is depicted (Alexander, Loomis and Lee Medical Clinics of North America, Sept, 1949)

Figure … was g… same … 5 per … operat… for glycosuria but the test for acetone … at this time … P M, 3 A M, … of 5 per cent … nt glucose in normal saline was used Reactions for glycosuria remained 2 plus or less and those for acetone remained negative in all specimens

By 3 P M March 10, liquid feedings could again be tolerated and a four meal diet similar to the preoperative diet was ordered Regular insulin was given, as usual, before each feeding Return to a three meal diet and long acting insulin was accomplished prior to discharge from the hospital

This case history illustrates the general management of a diabetic patient requiring major surgery. It demonstrates the preoperative four meal schedule used as the basic pattern during the operative and postoperative periods When it was impossible to use oral feedings, glucose solutions were given

intravenously, each infusion being started at the time when the meal would have been served. *Regular insulin administered subcutaneously* was used throughout the critical period and always at the beginning of a feeding or infusion. This case is unusual in that the dose of insulin did not need to be altered during the entire operative period. Also, the amount of fluid given was greater than would ordinarily be required.

*Choice of Anesthesia.* It is preferable to have a qualified anesthetist, who is familiar with the patient, to make the choice of the anesthetic. When practical le, *local* or *regional anesthesia* is desired. For amputations *spinal* anesthesia is our choice except in the occasional case in which the limb has been refrigerated (see p. 196). In this event no further anesthesia is necessary. For *general anesthesia* induction with gas-oxygen and continued with ether is eminently satisfactory. Nitrous oxide is the general anesthetic of choice for short operations and when good relaxation of the abdominal muscles is not a requisite.

*Every effort is made to avoid anoxia.* Morphine, if used, is given in minimal doses. Chloroform and ethyl chloride are contraindicated for diabetic patients.

## REFERENCES

1. Duncan, G. G., Carey, L. S., and Hudson, M. T.: M. Clin. North America (Nov.) 1949, p. 1537.
2. *National Research Council in Convalescence and Rehabilitation*, Report No. 1 (Feb.) 1944.
3. Alexander, J. B., Loomis, A. H., and Lee, C. T., Jr.: M. Clin. North America (Sept.) 1949, p. 1413.

CHAPTER XVII

# Diabetic Coma

**Introduction** The pathologic physiology of diabetic coma has been dealt with in Chapter VIII As an introduction to the practical features it suffices to say that (a) Diabetic coma is one of the greatest of medical emergencies (b) It is preventable (c) It does not develop while the diabetes is under good control (d) It is recognizable and may be readily corrected in its early stages (e) Deaths from diabetic coma have been reduced dramatically but they still occur because of ignorance delay and neglect (f) Fatalities may occur from hypopotassemia appearing as a complication of therapy for diabetic coma (g) Hypopotassemia* is readily detected by electrocardiographic studies and can be prevented or corrected by the oral administration of potassium chloride

The prompt detection of hypopotassemia and its correction is of new and important interest At the outset of therapy for diabetic coma as a rule there is a hyperpotassemia as indicated in the electrocardiographic record in Figure 30 but as therapy is carried out several processes which tend to reduce the concentration of potassium in the circulation are in operation These are the dilution factor the excretion of potassium in the urine the loss by vomiting inadequate intake the utilization of this electrolyte in the laying down of glycogen and of protein and other factors not clearly understood

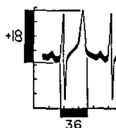
Potassium chloride can be given routinely as indicated in the outline of therapy There need be no concern of this therapy doing harm if urine is being excreted freely Anuria tends to prevent hypopotassemia The routine administration of potassium chloride should be omitted if the patient is anuric This is recommended for two reasons (1) because a hyperpotassemia may be precipitated and (2) because there is not likely to be a need for it during this period

An excellent review of the present status of potassium therapy has been published by Elkinton and Tarail[*]

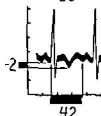
**Nature of Diabetic Coma and Its Diagnosis** Diabetic ketosis progressing until the patient is in a state of coma occurs when the utilization

* Potassium is present in normal serum in concentrations of 3.8 to 4.3 mEq/L. (14.8 to 16.8 mg/100 ml.)

of carbohydrate is reduced to a degree which causes an increase of great magnitude in the metabolism of fat As a result, acetone bodies (acetone, diacetic acid and beta hydroxybutyric acid) are produced at a rate which exceeds the ability of the body to complete their oxidation and the excess, in the early stages, is excreted in the urine As this process progresses 1 plus reactions for acetone in the urine are replaced by 2 plus, 3 plus, and finally 4 plus reactions The kidneys, and to a minor extent the lungs, can carry off, for variable periods, the excess acetone bodies from the blood but, bar-




SERUM K = 7 7
R R (SEC) = 64
CALC QT = 32




SERUM K = 3 1
R-R (SEC) = 56
CALC QT = 296

[illegible]

QT interval normal.
*Hypopotassemia* Lower tracing—serum K 3 1 mEq /L (12 mg /100 mL)
T wave inverted
QT interval prolonged

ring relief, finally acetone production exceeds the functional capacity of the excretory mechanisms and acetone bodies accumulate in the blood At first, this stage is detectable by the appearance of traces of acetone in the blood plasma but, if not corrected, 2 plus, 3 plus, and finally 4 plus qualitative reactions for plasma acetone are observed Usually, it is not until 4 plus reactions for acetone in the urine are observed for variable periods that amounts of acetone increase in the plasma to a sufficient concentration to be detected by the usual tests employed Hence, in general, a *3 or 4 plus reaction for acetone in the plasma indicates a much more advanced degree of ketosis than do similar reactions obtained on examination of the urine.*

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The prompt detection of hypopotassemia and its correction is of new and important interest At the outset of therapy for diabetic coma, as a rule, there is a hyperpotassemia, as indicated in the electrocardiographic record in Figure 30, but as therapy is carried out several processes which tend to reduce the concentration of potassium in the circulation are in operation These are the dilution factor, the excretion of potassium in the urine, the loss by vomiting, inadequate intake, the utilization of this electrolyte in the laying down of glycogen and of protein and other factors not clearly understood

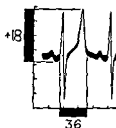
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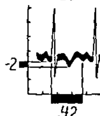
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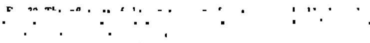
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* Potassium is present in normal serum in concentrations of 3 8 to 4.3 mEq/L (14 8 to 16 8 mg/100 ml)

of carbohydrate is reduced to a degree which causes an increase of great magnitude in the metabolism of fat. As a result, acetone bodies (acetone, diacetic acid and beta hydroxybutyric acid) are produced at a rate which exceeds the ability of the body to complete their oxidation and the excess, in the early stages, is excreted in the urine As this process progresses 1 plus reactions for acetone in the urine are replaced by 2 plus, 3 plus, and finally 4 plus reactions The kidneys, and to a minor extent the lungs, can carry off, for variable periods, the excess acetone bodies from the blood but, bar-



T wave—increased amplitude with a narrow base
QT interval normal.
*Hypopotassemia* Lower tracing—serum K 3 1 mEq /L.
(12 mg /100 ml.)
T wave inverted
QT interval prolonged

ring relief, finally acetone production exceeds the functional capacity of the excretory mechanisms and acetone bodies accumulate in the blood At first, this stage is detectable by the appearance of traces of acetone in the blood plasma but, if not corrected, 2 plus, 3 plus, and finally 4 plus qualitative reactions for plasma acetone are observed Usually, it is not until 4 plus reactions for acetone in the urine are observed for variable periods that amounts of acetone increase in the plasma to a sufficient concentration to be detected by the usual tests employed Hence, in general, a *3 or 4 plus reaction for acetone in the plasma indicates a much more advanced degree of ketosis than do similar reactions obtained on examination of the urine.*

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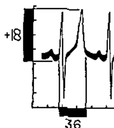
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[illegible]

| | |
|---|---|
| | T wave—increased amplitude with a narrow base |
| | QT interval normal |
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| | (12 mg /100 ml.) |
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Potassium chloride can be given routinely as indicated in the outline of therapy There need be no concern of this therapy doing harm if urine is being excreted freely Anuria tends to prevent hypopotassemia The routine administration of potassium chloride should be omitted if the patient is anuric This is recommended for two reasons (1) because a hyperpotassemia may be precipitated, and (2) because there is not likely to be a need for it during this period

An excellent review of the present status of potassium therapy has been published by Elkinton and Tarail[2]

**Nature of Diabetic Coma and Its Diagnosis.** Diabetic ketosis progressing until the patient is in a state of coma, occurs when the utilization

* Potassium is present in normal serum in concentrations of 3 8 to 4.3 mEq /L. (14 8 to 16 8 mg /100 mL)

of carbohydrate is reduced to a degree which causes an increase of great magnitude in the metabolism of fat. As a result, acetone bodies (acetone, diacetic acid and beta hydroxybutyric acid) are produced at a rate which exceeds the ability of the body to complete their oxidation and the excess, in the early stages, is excreted in the urine. As this process progresses 1 plus reactions for acetone in the urine are replaced by 2 plus, 3 plus, and finally 4 plus reactions. The kidneys, and to a minor extent the lungs, can carry off, for variable periods, the excess acetone bodies from the blood but, bar

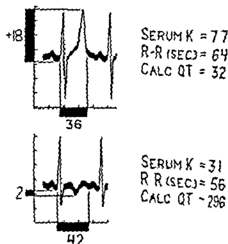



Fig 30 The influences of the concentration of potassium in the blood on electrocardiographic records are illustrated in precordial lead CR₄. (After [illegible] et al.)

*Hyperpotassemia* Upper tracing—serum K 7.7 mEq./L. (30 mg./100 ml.) T wave—increased amplitude with a narrow base QT interval normal.

*Hypopotassemia* Lower tracing serum K 3.1 mEq./L. (12 mg./100 ml.) T wave inverted (QT interval prolonged)

ring relief finally acetone production exceeds the functional capacity of the excretory mechanisms and acetone bodies accumulate in the blood. At first, this stage is detectable by the appearance of traces of acetone in the blood plasma but, if not corrected, 2 plus, 3 plus, and finally 4 plus qualitative reactions for plasma acetone are observed. Usually, it is not until 4 plus reactions for acetone in the urine are observed for variable periods that a [illegible] acetone increase in the plasma to a sufficient concentration to [illegible] employed. Hence, in [illegible] 3 or 4 plus [illegible]

o) ne [illegible]

The diabetic patient having 4 plus reactions for glycosuria and acetonuria, and a 4 plus reaction for plasma acetone fulfills *the chemical criteria* necessary to make the diagnosis of diabetic coma The diagnosis can be made at the bedside Urine for testing is obtained by catheter if necessary and 10 cc of oxalated blood allowed *to stand for a few minutes will provide* plasma or serum, of which only one drop is needed in the test for acetone (see p 69)

Excessive production of ketones *provides the clue to the diagnosis and* the early detection of this clue is of extraordinary importance The simplicity of the tests for acetone in the plasma puts a precise and valuable diagnostic *measure in the hands of every physician The diagnosis can be* established without elaborate equipment or technical assistance and—of most importance—therapy can be started at once It is practicable then, *even in remote places, to give a patient in diabetic coma the opportunities* of recovery closely approaching those enjoyed by patients in large cities with nearby hospital facilities In case of the latter group their chances of *recovery from diabetic coma are also greatly enhanced if the diagnosis is* made in the home and not delayed until the patient is admitted to the hospital We know of a patient in whose case the diagnosis was made and *100 units of insulin and 8 ounces of well salted broth were given within* thirty minutes of the time the physician saw the patient This illustrates what can be the next great advance in the management of diabetic coma—*immediate diagnosis with insulin and sodium chloride administration* begun in all cases preliminary to moving the patient to the hospital

Prior to and in the early stages of ketosis important disturbances in the patient's *fluid and electrolyte balances have been taking place, notably the* increased hyperglycemia with its diuretic effect, the loss in the urine of large quantities of sugar and of base, especially sodium and to a smaller degree *but nevertheless of great importance, potassium All have a bearing* on the clinical state of the patient and on the therapy necessary These later considerations account for the intense dehydration, hemoconcentration increased specific *gravity of the whole blood, low, and at times imperceptible* blood pressure, vascular collapse with evidences of the resulting renal incompetence as indicated in the gravely ill patient by oliguria with albumin and *granular casts, or in some instances by anuria with the development* of the uremic state, if correction is delayed If the shocklike state prevails for many hours, changes in the renal tubules characteristic of a lower nephron nephrosis may *occur In these rare cases the excessive administration* of fluids is fraught with great danger

Second only in importance to an *early diagnosis* and *insulin therapy* are the halting and correction of *these secondary and dangerous processes Administration of salty broth, orally, as soon as the diagnosis is made will often turn the tide favorably and in some cases will be life saving* Most medical writings deal almost exclusively with diagnosis and treatment of

coma in hospitalized patients This communication stresses also what can be done in the field so to speak, or, as it were, at the front line before evacuating the patient to the hospital

**Precipitating Causes of Diabetic Coma** Any factor or factors which increase total tissue metabolism with one exception—physical exercise—tend to intensify the diabetes and as a result increase the need for insulin Illustrations of this effect are observed in cases of thyrotoxicosis, pregnancy, febrile disturbances and gain in body weight A diagrammatic illustration of the reduction in the effectiveness of insulin during acute complications is presented in Figure 27

The unfavorable influence of increasing total metabolism alone or when combined with other features which predispose to and cause diabetic coma may precipitate a clinical emergency with great rapidity The pregnant and the thyrotoxic diabetic patients who develop acute infections illustrate this group, as do the neglected obese diabetic patients who acquire staphylococcic skin infections, notably carbuncles Also, the patient who disregards —by ignorance or indifference—dietary restrictions and overeats, with the result that the diabetes is out of control is predisposed to develop ketosis when a precipitating factor makes its appearance He is a candidate for a rapidly developing ketosis in the event of infections even of a minor nature gastro intestinal disturbances (vomiting or diarrhea), surgical complications and the omission of insulin It is remarkable how frequently the diabetic patient, because of anorexia during an acute complication, omits insulin This may be done with or without the advice of a physician In such cases the anorexia is frequently due to ketosis in its early stages and all that remains to speed the quickest possible development of coma is the withdrawal of insulin therapy The anorexic diabetic patient is a potential emergency at all times but when the anorexia is associated with some other disorder, be it an upper respiratory tract infection, gastro intestinal upset or one of the possible multitude of complications, the emergency exists and careful clinical evaluation and therapy are necessary if needless risk is to be avoided Such patients who exhibit strongly positive reactions for glycosuria and acetonuria and whose plasmas give a 2 plus or 1 plus reaction for acetone are in the pre coma state

The anorexia of the diabetic patient suffering from an acute clinical condition is intensified by nausea and, with the onset of vomiting and its unfavorable influence on the fluid balance and chloride depletion, the dehydration and vascular collapse in these patients are quickened

Sodium chloride administered as salty broth in the anorexic phase may halt and will certainly postpone the downward progress We have repeatedly observed that this simple measure has alleviated nausea, and vomiting often ceases when salty broth is ingested Failing an early diagnosis or early treatment or both the ketosis gains headway slowly—several days to weeks —in the neglected diabetic without acute complications, but the ketosis de-

velops very rapidly—a matter of hours—in the presence of acute infection and toxemia

**Prevention** Diabetic coma is preventable but to achieve this goal patients must be trained thoroughly concerning (a) the factors which precipitate coma, (b) the speed with which coma may develop and (c) the manner in which the early symptoms are manifested Also, we must make earlier diagnoses, provide adequate therapy and safeguard against over treatment if this complication is to be prevented, and corrected with minimum risk if it is already established

Patients should be aware of the benign course which controlled diabetes pursues and the upheaval that can come with great rapidity with an acute infection It is remarkable how many patients test the urine regularly for sugar only until they feel badly and, by discontinuing tests with the onset of a complication, deprive themselves of the only real clue that they understand, namely, strongly positive reactions for glycosuria Following in rapid succession come the anorexia, nausea and often vomiting The speed with which these patients may pass into the danger zone cannot be over emphasized

With adequate training diabetic patients make provision for *testing the urine* in the event of illness and they will always regard *loss of appetite* with or without *nausea* in the presence of *strong reactions for glycosuria* as danger signals concerning the correction of which their physician should be consulted Also, the patient should know that in the anorexic phase insulin must not be omitted if strongly positive reactions for glycosuria are present The pre-coma state should be suspected under these circumstances In case this suspicion is confirmed by a 4 plus reaction for glycosuria and acetonuria and a 1 or 2 plus reaction for plasma acetone, small frequently administered doses (every four hours) of regular insulin are indicated The amounts are regulated according to the changes in the degree of glycosuria In these instances the administration of salty broth by mouth will usually alleviate the nausea and permit frequent administration of carbohydrate by mouth which, with the accompanying insulin therapy, will quickly correct the early ketosis *Too little attention has been given in medical literature to the value of sodium chloride in dealing with the pre coma state*

In the event that the acute complication which is precipitating the ketosis is not correctable promptly—within a matter of hours—the danger of ketosis can be reduced and the control of the diabetes can be more exactly regulated by prescribing the diet in four equal feedings—one every six hours —and regular insulin—one fourth of the former total insulin dosage plus a modest increase—before each feeding making adjustments according to the effect on the glycosuria in the respective six hour fractions We have used and advocated this principle of treatment for many years It has received widespread acceptance Illustrative insulin regimens are presented in Table 34, page 217

A liquid diet divided into four equal feedings which has been found to be satisfactory is presented in Diet XII When regular foods are tolerated a diet as illustrated in Diet XIII, may be employed until the routine diet and insulin may be resumed after the acute complication has subsided

**Treatment** Therapy is directed at the fundamental faults by giving insulin frequently and in adequate amounts, by restoring fluids and electrolytes until normal values prevail, and by providing adequate carbohydrate to permit a reduction in fat metabolism and to replenish depleted glycogen stores Other, but secondary, therapeutic measures are included in the following outline of treatment for diabetic coma employed at the Pennsylvania Hospital

**Outline of Treatment for Diabetic Coma** The working diagnosis of diabetic coma is made when 4 plus glycosuria, 4 plus acetonuria, and 4 plus plasma acetone are found in the case of an acutely ill patient When these findings are present

I Begin treatment immediately

Insulin (regular)—40 units intravenously*
60 units subcutaneously

Fluids and Chlorides—2000 cc normal saline are given intravenously (give rapidly—15 to 20 cc per minute—if systolic blood pressure is below 90 mg Hg)†

II Studies—Secure immediately

(1) Blood for sugar content, acetone bodies, hematocrit $CO_2$ combining power, specific gravity (whole blood), and urea determinations

(2) Urine for culture and routine complete analysis

III The Director of the Medical Division or, failing to reach him, a senior assistant will be notified promptly by the medical resident of the admission of a patient in diabetic coma The resident will also alert the Laboratory for emergency studies Also, arrangement for full time service of a resident and nurse should be made until the patient's life is out of danger

IV Secure urine at two hour intervals‡ for sugar and acetone determinations until the ketosis is corrected

V Secure blood specimens at four hour intervals, day and night, for acetone, $CO_2$ and sugar and specific gravity (whole blood) until

* With the exception of this initial dose all insulin is administered subcutaneously

† Heat should not be applied to patients in diabetic coma as the peripheral vasodilatation which it causes may intensify the shocklike state Normal room temperatures are quite satisfactory

‡ A retention catheter may be used for this purpose when necessary Utmost care [illegible] in twenty four hours. Immediately prior to removal of catheter a urine specimen for culture is obtained.

the patient is conscious and retaining nourishment by mouth Subsequent studies as conditions indicate

VI Secure an electrocardiogram as early as is practicable and repeat at four hour intervals for twenty four hours More frequent tracings are indicated to guide therapy in cases of *hypopotassemia*

VII Treatment During Critical Phase Subsequent to the Preliminary Measures Outlined in I

Immediately upon receiving confirmative reports on the blood sugar value and the plasma CO combining power, or within one hour of making the diagnosis whichever is earlier, begin

Insulin (regular) 50 units subcutaneously at one-half hour intervals *until* an appreciable reduction of the plasma acetone or increase in the $CO_2$ combining power is noted Increases above these amounts will rarely be necessary, but if no decrease in plasma acetone or increase in $CO_2$ combining power of the blood plasma *has occurred after six hours* of therapy each succeeding dose may* be increased by 25 units until such changes are noted Dangers of a rapidly developing hypoglycemia will be avoided by giving glucose (1 liter of 5 per cent solution) intravenously after six hours of therapy (see Par X) or carbohydrates orally, if practicable

VIII When to Reduce Insulin

*An appreciable reduction of the plasma acetone and an appreciable* increase of the $CO_2$ combining power of the blood plasma coincide with a lessening of the resistance to insulin Such findings should put the physician on the alert to the possibility of a rapidly developing hypoglycemia When the clinical condition and laboratory findings indicate that the patient is showing satisfactory progress the insulin dosage schedule on an hourly and later two or three hour basis may be guided as follows

4 plus glycosuria—30 units
3 plus glycosuria—reduce to 20 units
*2 plus glycosuria—reduce to 10 units*
1 plus glycosuria—omit dose
0 glycosuria—omit dose of insulin and give 20 gm carbohydrate

The reduction of plasma acetone to a trace or an increase of the $CO_2$ combining power to a value above 40 volumes per cent is if the clinical condition of the patient permits indication for insulin and diet at six hour intervals *(see Par XIII)*

IX Fluids and Salts

Loss of electrolytes and fluids to a marked degree occurs in the

* It is usual to find little change in the blood findings in the first four hours but by the end of six hours improvement should be noted unless unusual circumstances are present

development of diabetic coma Correction of these deficiencies at the earliest opportunity is imperative This is done properly by the intravenous administration of physiologic saline solution, in amounts of 2000 to 3000 cc within the first two hours of treatment Further administration is given freely while the specific gravity of the whole blood remains above 1.055 while the hematocrit values remain above 50 per cent and the systolic blood pressure remains below 90 mm Hg As soon as the patient's condition permits, broths and carbohydrate containing fluids—strained cereal gruel, ginger ale (non-effervescent) sweetened tea and later fruit juices —may be given Potassium chloride,* 1 gm every four hours for five doses is given routinely to the adult patient after four hours of therapy provided urine is being excreted freely Relatively smaller amounts are given to children Accurate records of fluid intake and output are essential

X Carbohydrate

Glucose 1000 cc of a 5 per cent solution in normal saline, is given intravenously beginning six hours after the first dose of insulin is given if at this time liquids given orally are not retained This is repeated in six hours if the patient is not taking or retaining nourishment by mouth

XI Alkali

The administration of alkali usually is not necessary However, an amount of racemic sodium lactate sufficient to raise the $CO_2$ combining power to a relatively innocent level—30 volumes per cent—will relieve air hunger rapidly Larger amounts are contraindicated The foregoing amount of alkali is permissible also for the critically ill patient having a plasma $CO_2$ combining power below 15 volumes per cent A transfusion using whole blood is an efficient means of restoring both base and blood volume

XII Gastric Lavage—Enema

The stomach should be emptied of its contents in cases of abdominal distention abdominal pain or vomiting Eight ounces of warm normal saline solution are left in the stomach An enema is indicated in nearly every case of coma It may be delayed until improvement in the patient's condition is noted

XIII Diet

When evidences of acute ketosis have subsided, a liquid diet is allowed for twelve to twenty four hours and thereafter a "house diet" of the same values for example, protein 110 gm fat 65 gm., and carbohydrate 250 gm (2000 calories) The diet is given in

* If indications of hypopotassemia are not corrected promptly by the oral administration of potassium chloride give 100 to 500 cc of a 1.12 per cent solution intravenously slowly until a satisfactory electrocardiographic response is observed

TABLE 36
DIABETIC COMA—STUDIES AND THERAPY RECORD
Pennsylvania Hospital

Date________ Half Day of Treatment________ Name________________ U H No.____
Time________

| Hours of Treatment | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| STUDIES | | | | | | | | | | | | | |
| Blood Sugar | * | | | | * | | | | * | | | | * |
| Acetone | * | | | | * | | | | * | | | | * |
| $CO_2$ | * | | | | * | | | | * | | | | * |
| Hematocrit | * | | | | * | | | | * | | | | * |
| Specific Gravity | * | | | | * | | | | * | | | | * |
| Urea Nitrogen | * | | | | | | | | | | | | * |
| Urine Sugar | * | | * | | * | | * | | * | | * | | * |
| Acetone | * | | * | | * | | * | | * | | * | | * |
| Culture | * | | | | | | | | | | | | |
| Analysis | * | | | | | | | | * | | | | |
| Electrocardiogram | * | | | | * | | | | * | | | | * |
| Blood Pressure | * | * | * | * | * | | * | | * | | * | | * |
| Other | | | | | | | | | | | | | |
| THERAPY | | | | | | | | | | | | | |
| Regular Insulin | | | | | | | | | | | | | |
| *Intake—I V Fluids* Normal saline | | | | | | | | | | | | | |
| Dextrose, 5% in D/W | | | | | | | | | | | | | |
| Dextrose, 5% in N/S | | | | | | | | | | | | | |

| Hours of Treatment | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Sodium R lactate Soln | | | | | | | | | | | | | |
| Blood Whole | | | | | | | | | | | | | |
| Plasma | | | | | | | | | | | | | |
| Potassium Chloride | | | | | | | | | | | | | |
| Other Solutions | | | | | | | | | | | | | |
| INTAKE *Subcutaneous Fluids* | | | | | | | | | | | | | |
| *Oral* | | | | | | | | | | | | | |
| OUTPUT Urine | | | | | | | | | | | | | |
| Vomitus | | | | | | | | | | | | | |
| Gastric Lavage | | | | | | | | | | | | | |
| Feces | | | | | | | | | | | | | |
| Enema | | | | | | | | | | | | | |
| Other | | | | | | | | | | | | | |
| MEDICATIONS Oral KCl | | | | | | | | | | | | | |
| Penicillin | | | | | | | | | | | | | |
| Other Antibiotics | | | | | | | | | | | | | |
| Vitamin B Complex | | | | | | | | | | | | | |
| MISCELLANEOUS | | | | | | | | | | | | | |

four equal feedings, one every six hours; and finally, with complete recovery from the attack, the diet and insulin regimens as for the uncomplicated diabetic patient are resumed.

**Case Report.** The case report of a patient treated recently for diabetic coma is presented It illustrates many of the features already touched upon in this communication and others that will be dealt with in chronological order.

E. D, a Negress aged thirty six years, was admitted in a profound coma to the Pennsylvania Hospital on March 4, 1949 Relatives stated that the patient was three

TABLE 37

SUMMARY OF LABORATORY DATA AND THERAPY (PATIENT E D)

| DATE | BLOOD | | | | | | URINE | | |
|---|---|---|---|---|---|---|---|---|---|
| 3/4/49 | Sugar mg / 100 cc | CO vol per cent | Acetone in plasma | Urea mg / 100 cc | Hematocrit per cent | Sp Gr | Sugar | Acetone | Amount (cc) |
| 11 00 A M | 1452 | 12 | ++++ | 38 | 51 | | ++++ | ++++ | 300 |
| 1 00 P M | 1372 | 16 | ++++ | | 48 | 1 066 | ++++ | ++++ | 135 |
| 3 00 P M | 861 | 18 | ++++ | 31 | 38 | 1 039 | ++++ | ++++ | 700 |
| 5 00 P M | 834 | | ++++ | | 41 | 1 039 | ++++ | ++++ | 1125 |
| 7 00 P M | | 33 | ++++ | | 32 | | +++ | ++++ | 775 |
| 9 00 P M | 377 | | ++++ | | 35 | | + | ++++ | 150 |
| 11 30 P M | 291 | | ++++ | | 35 | | 0 | ++++ | 175 |
| | | | | | | | First 12 hours | | 3360 |
| 1 30 A M | 287 | | +++ | | 37 | | 0 | ++++ | 150 |
| 3 30 A M | 324 | | ++ | | 35 | | + | +++ | — |
| 5 30 A M | 251 | 49 | + | | | | 0 | + | — |
| 9 00 A M | 186 | | + | 26 | 36 | | + | + | 300 |
| | | | | | | | Second 12 hours | | 450 |
| | | | | | | | 24 Hour Totals | | 3810 |

Total fluids administered First 12 hours 8 730 cc —intravenously
Second 12 hours 3 900 cc —orally
Total insulin administered First 12 hours 1 350 units
Second 12 hours 400 units

months postpartum and that since the delivery and following a "cold" she had complained of excessive thirst and appetite and the frequent passing of large amounts of urine and that she had lost weight from 246 pounds to 211 pounds in this period The family doctor had made the diagnosis of diabetes one week before her admission but his advice to seek hospital care went unheeded The patient had no appetite for food on the day prior to admission and toward evening she had "difficulty getting enough breath" At 4 00 A M on the day of admission she was found to be unconscious and could not be aroused

On admission a catheterized specimen of urine gave *4 plus reactions for glycosuria and acetonuria and there was a 4 plus reaction for plasma acetone* The criteria for diabetic coma being fulfilled, insulin was given at once—50 units of regular insulin intravenously and 50 units of regular insulin subcutaneously Also, an intravenous

infusion of normal saline was begun. Chemical studies of the initial specimen of blood revealed a blood sugar level of 1152 mg. per 100 cc. and a $CO_2$ combining power of the plasma of 12 volumes per cent.

The physical examination revealed the profound state of coma, marked obesity, a severe degree of dehydration, and typical Kussmaul breathing also of a severe degree. The tongue was red and dry and the conjunctival reflexes were absent. The blood pressure was 95 mm. Hg systolic and 50 diastolic, the pulse rate 156 and the body temperature 102° F. (rectal). Otherwise the physical findings were not remarkable. The lungs were clear and there was no distention of the abdomen. Laboratory findings summarized in Table 37 show: Plasma sugar 1152 mg. per 100 cc., plasma acetone 4 plus, $CO_2$ combining power 12 volumes per cent, blood urea nitrogen 38 mg. per 100 cc., glycosuria and acetonuria 4 plus, albuminuria 2 plus, and many granular casts in the urine. The leukocyte count was 17,650 per cu. mm. of blood. There were 5,080,000 red cells per cu. mm., the hematocrit reading was 51 per cent and the specific gravity of the whole blood was 1.066.

*Insulin.* Insulin, with the exception of 200- and 100-unit doses administered early in the treatment, was given in doses of 50 units every half hour until the blood sugar was reduced to 377 mg. per 100 cc. The totals amounted to 1350 units in the first twelve hours of therapy and 1750 units in the first twenty-four hours. This amount of insulin far exceeds the quantity usually necessary to correct ketosis. It will be observed in Table 37 that there are no evidences that excessive amounts of insulin were given nor were there, at any time, clinical signs of overdosage. It was considered of utmost importance that large amounts of insulin be given frequently with ample carbohydrate as long as 4 plus reactions for plasma acetone were found. As the concentration of plasma acetone decreases the sensitivity to insulin increases, hence a lessening of the amounts of insulin as well as a reduced frequency of administration are imperative if hypoglycemic reactions are to be prevented.

*Fluids.* An extreme degree of dehydration was clinically manifest, the blood pressure was 95 mm. Hg systolic and 50 mm. diastolic and the specific gravity of the whole blood was 1.066 (normal 1.052 to 1.058). These studies when repeated indicated that despite the administration of unusually great amounts of fluids—2700 cc. of normal saline in the first two hours of therapy and 6200 cc. in the first six hours—the specific gravity of the whole blood was still elevated—1.059. Nevertheless with progress being otherwise favorable the rate of the administration of fluid was sharply reduced. The total volume of fluids—normal saline, plasma and glucose in distilled water—given in the first twelve hours reached a total of 8730 cc. In the second twelve hours of treatment fluids given by mouth amounted to 3900 cc., bringing the total in the first twenty-four hours to 12,600 cc. Less fluid in this latter period might have sufficed but with a urine volume of only 450 cc. a smaller fluid intake was not justified. Also, dehydration was still manifest. The large output of urine in the first twelve hours was not attributable to excess fluid intake but rather to the diuretic influence of the hyperglycemia which prevailed. When this was alleviated the positive water balance was enhanced.

four equal feedings, one every six hours, and finally, with complete recovery from the attack, the diet and insulin regimens as for the uncomplicated diabetic patient are resumed

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| 3 00 P M | 864 | 18 | ++++ | 34 | 38 | 1 059 | ++++ | ++++ | 700 |
| 5 00 P M | 834 | | ++++ | | 41 | 1 059 | ++++ | ++++ | 1125 |
| 7 00 P M | | 33 | ++++ | | 32 | | +++ | ++++ | 775 |
| 9 00 P M | 377 | | ++++ | | 35 | | + | ++++ | 150 |
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*Fluids* An extreme degree of dehydration was clinically manifest the blood pressure was 95 mm Hg systolic and 50 mm diastolic and the specific gravity of the whole blood was 1 066 (normal 1 052 to 1 058) These studies when repeated indicated that despite the administration of unusually great amounts of fluids—2700 cc of normal saline in the first two hours of therapy and 6200 cc in the first six hours—the specific gravity of the whole blood was still elevated—1 059 Nevertheless with progress being otherwise favorable the rate of the administration of fluid was sharply reduced The total volume of fluids—normal saline plasma and glucose in distilled water—given in the first twelve hours reached a total of 8730 cc In the second twelve hours of treatment fluids given by mouth amounted to 3900 cc., bringing the total in the first twenty four hours to 12 600 cc Less fluid in this latter period might have sufficed but with a urine volume of only 450 cc a smaller fluid intake was not justified Also, dehydration was still manifest The large output of urine in the first twelve hours was not attributable to excess fluid intake but rather to the diuretic influence of the hyperglycemia which prevailed When this was alleviated the positive water balance was enhanced

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TABLE 37

SUMMARY OF LABORATORY DATA AND THERAPY (PATIENT E D)

| DATE | BLOOD | | | | | | URINE | | |
|---|---|---|---|---|---|---|---|---|---|
| 3/4/49 | Sugar mg / 100 cc | $CO_2$ vol per cent | Acetone in plasma | Urea mg / 100 cc | Hematocrit per cent | Sp Gr | Sugar | Acetone | Amount (cc) |
| 11 00 A M | 1452 | 12 | ++++ | 38 | 51 | | ++++ | ++++ | 300 |
| 1 00 P M | 1372 | 16 | ++++ | | 48 | 1 066 | ++++ | ++++ | 135 |
| 3 00 P M | 864 | 18 | ++++ | 34 | 38 | 1 059 | ++++ | ++++ | 700 |
| 5 00 P M | 834 | | ++++ | | 41 | 1 059 | ++++ | ++++ | 1125 |
| 7 00 P M | | 33 | ++++ | | 32 | | +++ | ++++ | 775 |
| 9 00 P M | 377 | | ++++ | | 35 | | + | ++++ | 150 |
| 11 30 P M | 291 | | ++++ | | 35 | | 0 | ++++ | 175 |
| | | | | | | | First 12 hours | | 3360 |
| 1 30 A M | 287 | | +++ | | 37 | | 0 | ++++ | 150 |
| 3 30 A M | 324 | | ++ | | 35 | | + | +++ | — |
| 5 30 A M | 251 | 19 | + | | | | 0 | + | — |
| 9 00 A M | 186 | | + | 26 | 36 | | + | + | 300 |
| | | | | | | | Second 12 hours | | 450 |
| | | | | | | | 24 Hour Totals | | 3810 |

Total fluids administered First 12 hours 8 730 cc—intravenously
Second 12 hours 3 900 cc—orally
Total insulin administered First 12 hours 1 350 units
Second 12 hours 100 units

months postpartum and that since the delivery and following a "cold" she had complained of excessive thirst and appetite and the frequent passing of large amounts of urine and that she had lost weight from 216 pounds to 211 pounds in this period The family doctor had made the diagnosis of diabetes one week before her admission but his advice to seek hospital care went unheeded The patient had no appetite for food on the day prior to admission and toward evening she had difficulty getting enough breath At 4 00 A M on the day of admission she was found to be unconscious and could not be aroused

On admission a catheterized specimen of urine gave *4 plus reactions for glycosuria and acetonuria and there was a 4 plus reaction for plasma acetone* The criteria for diabetic coma being fulfilled insulin was given at once—50 units of regular insulin intravenously and 50 units of regular insulin subcutaneously Also an intravenous

infusion of normal saline was begun. Chemical studies of the initial specimen of blood revealed a blood sugar level of 1452 mg. per 100 cc. and a $CO_2$ combining power of the plasma of 12 volumes per cent.

The physical examination revealed the profound state of coma, marked obesity, a severe degree of dehydration and typical Kussmaul breathing, also of a severe degree. The tongue was red and dry and the conjunctival reflexes were absent. The blood pressure was 95 mm. Hg systolic and 50 diastolic, the pulse rate 156 and the body temperature 102° F. (rectal). Otherwise the physical findings were not remarkable. The lungs were clear and there was no distention of the abdomen. Laboratory findings summarized in Table 37 show: Plasma sugar 1452 mg. per 100 cc., plasma acetone 4 plus, $CO_2$ combining power 12 volumes per cent, blood urea nitrogen 38 mg. per 100 cc., glycosuria and acetonuria 4 plus, albuminuria 2 plus, and many granular casts in the urine. The leukocyte count was 17,650 per cu. mm. of blood. There were 5,080,000 red cells per cu. mm., the hematocrit reading was 51 per cent and the specific gravity of the whole blood was 1.066.

*Insulin.* Insulin, with the exception of 200 and 100 unit doses administered early in the treatment, was given in doses of 50 units every half hour until the blood sugar was reduced to 377 mg. per 100 cc. The totals amounted to 1350 units in the first twelve hours of therapy and 1750 units in the first twenty four hours. This amount of insulin far exceeds the quantity usually necessary to correct ketosis. It will be observed in Table 37 that there are no evidences that excessive amounts of insulin were given nor were there, at any time, clinical signs of overdosage. It was considered of utmost importance that large amounts of insulin be given frequently with ample carbohydrate as long as 4 plus reactions for plasma acetone were found. As the concentration of plasma acetone decreases the sensitivity to insulin increases, hence a lessening of the amounts of insulin as well as a reduced frequency of administration are imperative if hypoglycemic reactions are to be prevented.

*Fluids.* An extreme degree of dehydration was clinically manifest, the blood pressure was 95 mm. Hg systolic and 50 mm. diastolic and the specific gravity of the whole blood was 1.066 (normal 1.052 to 1.058). These studies when repeated indicated that despite the administration of unusually great amounts of fluids—2700 cc. of normal saline in the first two hours of therapy and 6200 cc. in the first six hours—the specific gravity of the whole blood was still elevated—1.059. Nevertheless, with progress being otherwise favorable the rate of the administration of fluid was sharply reduced. The total volume of fluids—normal saline, plasma and glucose in distilled water—given in the first twelve hours reached a total of 8730 cc. In the second twelve hours of treatment fluids given by mouth amounted to 3900 cc., bringing the total in the first twenty four hours to 12,600 cc. Less fluid in this latter period might have sufficed but with a urine volume of only 150 cc. a smaller fluid intake was not justified. Also, dehydration was still manifest. The large output of urine in the first twelve hours was not attributable to excess fluid intake but rather to the diuretic influence of the hyperglycemia which prevailed. When this was alleviated the positive water balance was enhanced.

*Plasma* During the first hour of therapy the blood pressure decreased to a systolic pressure of 80 mm Hg the pulse rate became very rapid and eventually the pulse was imperceptible At this stage 350 cc of plasma was given A gradual increase in the blood pressure to 110 systolic and 70 diastolic ensued

*Alkali* Because of the intensity of the air hunger 600 cc of sodium racemic lactate solution was given intravenously A dramatic improvement followed The administration of alkali doubtless accounts to a considerable degree, for the elevation of the $CO_2$ combining power to 33 volumes per cent *while the plasma acetone bodies, not so appreciably affected by this* therapy, still gave 4 plus reactions This illustrates one means by which alkali therapy may, on the surface, be misleading

*Glucose* The intravenous administration of 5 per cent glucose solution —700 cc —was begun eight hours after therapy had been started This was necessary, as the blood sugar had been reduced to 291 mg per 100 cc while 4 plus reactions for plasma acetone still prevailed Subsequent carbohydrate intake was for the most part by the oral route

*Potassium* Electrocardiographic tracings were made at the onset of therapy and frequently thereafter Selected tracings of the second standard lead show a high T wave and a normal QT interval In contrast with later *electrocardiograms the high T wave was interpreted as indicating a hyper*potassemia—a common finding prior to insulin therapy and hydration in cases of diabetic coma A tracing four hours later shows a reduction in the amplitude of the T wave The QT interval remained unchanged At seven hours the T wave was still further depressed, suggesting the early stages of hypopotassemia Potassium chloride, 1 gm, was given orally at once and repeated every four hours for five doses The amplitude of the T waves was normal four hours after the onset of potassium chloride therapy and remained so—the electrocardiogram being repeated at twelve and twenty four hours respectively Prolongation of the QT interval in addition to progressive changes from reduced amplitude to flattening or even inversion of the T waves is a common indication of hypopotassemia (Fig 30) This change did not occur in this case Possibly the early detection and correction of the hypopotassemia prevented the development of this characteristic

*In retrospect, and from the experience of others, formerly unexplained* deaths in the second twelve hours of therapy in patients relieved of ketosis, and with no hypoglycemia, can surely be laid to hypopotassemia These patients, despite their satisfactory blood sugar and $CO_2$ combining power levels, were unduly weak and apprehensive and, with a rather sudden onset of paralysis of the respiratory muscles, death followed quickly Electrocardiographic tracings, taken frequently, afford an excellent means of detecting this dangerous complication hours before the clinical attack is likely to develop Holler's[3] patient developed paralysis of the respiratory

muscles and was in a respirator several hours when a very low serum potassium concentration was found. A dramatic recovery followed the administration of potassium chloride. Electrocardiograms present a much simpler method of detecting this abnormality than does quantitative analysis of the serum potassium. The work of Bellet and co-workers[4] has made this clear.

The current explanation of the development of *hyperpotassemia* is to the effect that during the intense dehydration potassium leaves the cells and with increased tissue protein breakdown hyperpotassemia and loss of potassium in the urine result. Hence, although the concentration of potassium in the serum is increased, the total body potassium is decreased.[2] But, when therapy is instituted the serum potassium is diluted, much is excreted with restoration of adequate hydration, cellular affinity for potassium is restored, and some potassium is used in the glycogen deposition in the liver and in association with protein deposition in the tissues. Hypopotassemia is likely to ensue.

*Penicillin.* Because of the unexplained fever, and of the prophylactic value of penicillin, this drug was given during the acute phase of the illness.

*Gastric Lavage.* This measure was not made use of, as there was no history of vomiting or abdominal pain and there was no distention of the abdomen. An enema was given after consciousness was restored.

*Progress Notes.* Improvements in the chemical values of the blood are noted in Table 37. Clinically, the recovery was slower than is usually observed. It was not until therapy had been carried out in an intensive manner for thirty four hours that the patient was fully aware of her surroundings, though after fifteen hours she gave indications of understanding what was said to her. However, though in a semistupor she was able to take fluids by mouth after twelve hours of treatment and a liquid diet with values of 110 gm. protein, 200 gm. carbohydrate and 95 gm. fat (2100 calories) was prescribed and given in four equal feedings—at six hour intervals. The insulin also was administered at six hour intervals. The diabetes was promptly controlled—fasting blood sugar value 86 mg. per 100 cc.—with the diet outlined above and with 180 units of insulin daily.

There being no evidence of an acute complication remaining on March 11, the seventh day of therapy, a reducing diet—100 gm. protein, 100 gm. carbohydrate and 22 gm. fat (1100 calories)—with supplementary minerals and vitamins was allowed. With this diet 110 units of insulin (80 units of protamine zinc and 30 units of regular insulin) daily maintained normal blood sugar values and freedom from glycosuria.

Pursuing our often repeated contention that an obese diabetic, and one who cannot attribute her obesity to insulin therapy, has a mild diabetes, and that obese patients are relatively insensitive to insulin, we did what one would not dare do in the case of a thin diabetic—we discontinued the 110 units of insulin abruptly on March 17 and gave none thereafter. Traces of

glycosuria occurred only on four occasions during the remainder of her hospital stay (eight days) and the fasting blood had increased only from 81 mg. (March 17) to 133 mg. (March 20). This patient was discharged on March 24 and when seen on the two succeeding weeks in the Out Patient Department she had reduced in weight an average of 1.9 kg. (4 lb.) per week. The blood sugar values were normal, the last being 117 mg. per 100 cc., and there was no sugar in any of the fractional urine collections. Subsequent progress has been equally satisfactory (Aug. 1950).

Comment. This case illustrates the following:

1. That even though the diabetes is mild an acute infection, even as mild as an upper respiratory tract infection, may precipitate a dangerous ketosis.

2. That anorexia was an outstanding symptom of the ketosis and that it followed a period of excessive appetite.

3. That a 3 plus reaction for plasma acetone accompanying a 4 plus reaction for glycosuria in a comatose patient verified the clinical diagnosis of diabetic coma before it was possible to know the blood sugar value and the $CO_2$ combining power of the plasma.

4. That the rapidly deepening state of shock was ameliorated by the administration of blood plasma.

5. That renal decompensation (indicated by the elevated blood urea nitrogen, the albuminuria and casts) developed with progression of the peripheral vascular collapse.

6. That unusually large doses of insulin are tolerated during profound ketosis.

7. That many liters of fluid were indicated and that the administration was carried out rapidly while the need was great, using the specific gravity* of the whole blood (with correction for the degree of hyperglycemia) as a reliable indicator. While the values were above 1.055 rapid administration was permissible but would not be considered essential if the blood pressure was well sustained and the hematocrit value was nearly normal. More fluid, by far, was given to this patient than is usually the case.

8. That a conservative amount (600 cc.) of 1/6 molar lactate solution promptly alleviated the intense degree of hyperpnea, and that despite this evidence of clinical improvement and an elevation of the $CO_2$ combining power to 33 volumes per cent, a 4 plus reaction for plasma acetone still maintained. This elevation of the $CO_2$ combining power is considered artificial and under these circumstances greater clinical value is placed on the qualitative (but crudely quantitative) reaction for plasma acetone. By testing serial dilutions of the plasma for acetone it is possible to secure a more accurate evaluation of the amount of ketones retained in the blood.

9. That glucose therapy was withheld for eight hours because of the

* Determined by the falling drop method. A simple method of determining this value using varying concentrations of copper sulfate solution has been widely used.

severe degree of hyperglycemia It is not considered that glucose given earlier would have been harmful but that it was unnecessary is obvious

10 That hypopotassemia which is prone to develop as treatment progresses, is detectable with adequate clinical accuracy by electrocardiographic studies and that this dangerous abnormality is readily corrected by the oral administration of potassium chloride It is quite probable that the degree of diuresis influences the risk of hypopotassemia We suggest the routine use of potassium chloride given by mouth when renal excretion is good but withhold it in the event of oliguria or anuria unless there are electrocardiographic evidences of hypopotassemia If the urgency demands potassium chloride may be given slowly intravenously—100 to 500 cc of a 1 14 per cent solution—or subcutaneously

11 That the uncomplicated obese diabetic can tolerate large amounts of insulin—in this case 110 units—which can be abruptly withdrawn with minor elevation of the blood sugar resulting while the patient is receiving a low calorie diet which, if continued brings the diabetes under perfect control

## REFERENCES


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CHAPTER XVIII

# Pregnancy Complicating Diabetes

*Introduction.* In the pre insulin eras pregnancy was infrequent in diabetic patients and if conception did occur gestation rarely proceeded to full term with a viable baby and without grave risks to the mother But, with insulin therapy, and all that it permits, pregnancy is no longer uncommon It carries little, if any, greater risk to the life of the diabetic mother than to non diabetic controls and the frequency with which full term viable babies are secured has increased greatly But, stillbirths remain approximately six times as frequent with diabetic mothers as occurs with nondiabetics (White) It is to be noted, too, that although the mothers come through pregnancy without the former risk to life they are predisposed to eclampsia, hypertensive and renal disease, hydramnios and irritability of the uterus Notwithstanding the progress that has been made, diabetes because of the degenerative changes associated with it and notably arterial and renal disease, and the tendency to hormonal imbalance, exerts far reaching effects on the course of pregnancy Pregnancy, in these cases, is not a contract to be entered upon lightly, but barring the hazards of a diabetes of over twenty years' duration, premature arterial disease, hormonal disturbances which can to a large extent be neutralized, and the unpredictable congenital anomalies, the outcome is likely to be satisfactory A satisfactory outcome depends considerably on the control of the diabetes, the adequacy of the diet, hormonal therapy when indicated, and the wise selection of the means of terminating the pregnancy

**The Diabetic Mother.** *Menstrual Irregularities* Delayed development of secondary sexual characteristics, amenorrhea, irregular menstruation meno and metrorrhagia, and an early menopause are frequent in women with untreated or poorly controlled diabetes However, with good control of the diabetes, catamenia is apt to occur at a normal age, or returns after a few months of amenorrhea, if the latter has been due to uncontrolled diabetes In general, adequate control of the diabetes brings about a normal menstrual cycle in the great majority of these patients

*Fertility* Poorly controlled diabetes militates against conception but with better management of the diabetic patient fertility is improved Despite this improvement diabetic women are somewhat less fertile than nondia

betics Nutritional deficiencies associated with uncontrolled diabetes are probably a big factor in the production of sterility Disturbances in hormonal relationships, especially a decrease in the amount of gonadotropic hormone of the anterior pituitary gland, are also considered to be important influences

*Abortion and Miscarriage Abortion and miscarriage are directly proportional to the lack of control of the diabetes* They occurred in 33 per cent of a series of uncontrolled diabetic patients, as compared with 2 per cent in patients whose diabetes was well controlled (White)



Fig 31 Calcified pelvic arteries in a diabetic woman fifty years of age.

*Stillbirths and Toxemia* Stillbirths are, despite insulin therapy, six times more common in diabetic than in nondiabetic women Factors that operate to produce this are the tendency of the babies of diabetic women to be overweight, and also the remarkable frequency of hydramnios in these women Diabetic patients are predisposed to toxemia by the prevalence of arteriosclerosis and of hypo-ovarianism which result in abnormalities of the sex hormones (excess serum chorionic gonadotropin) Calcification of the pelvic arteries (Fig 31), though not common, increases greatly the likelihood of stillbirths

*Abnormalities of Diabetic Pregnancies* Vascular diseases and hypo-ovarianism are the most common abnormalities affecting the diabetic mothers. White[1] found evidences of vascular disease (coronary artery disease, calcified vessels, retinopathies and nephritis) in 70 per cent of her

patients whose diabetes began in childhood and was of twenty years' duration or more Her rule for estimating the effect of the diabetes on the patient from an obstetrical point of view is as follows Up to five years' duration of diabetes, the obstetrical diabetic patient can be considered the same as a nondiabetic as far as vascular disease goes If the duration of the diabetes is five to fifteen years the amount of vascular disease to be expected makes the patient's physical age equal to the duration of the diabetes added to her actual age If the diabetes is of fifteen or more years' duration, the chronological age is doubled to get the patient's physical age Because of the serious vascular disease present in diabetic patients whose disease is of long standing, White[8] advises against pregnancy in a diabetic woman over thirty years of age, whose diabetes has been present twenty five years or more

As a result of the hypo ovarianism which, like vascular disease, increases in severity with the duration of the diabetes high levels of follicle stimulating hormone in the blood and low levels of 17 ketosteroid excretion in the urine are apt to develop The result is that diabetic women tend to be gynecologically older than their stated age

Chemical abnormalities of diabetic pregnancies are a low renal threshold for dextrose, and a disturbance of water balance The low renal threshold which is physiologic in pregnancy and has been reported in 35 to 60 per cent of all pregnancies, can result in the excretion of large amounts of glucose in the urine while the blood sugar levels remain within normal range When less than 100 grams of glucose are utilized daily, ketosis may result The disturbance of water balance is shown by an excessive gain in weight followed by edema hydramnios and fetal edema

*Mortality* (a) Maternal In the pre insulin era, the maternal mortality was between 25 and 30 per cent, but now the maternal mortality, when the diabetes is properly controlled, is no higher than the 0 6 per cent which occurs in nondiabetic controls *There is no excuse for diabetes in itself being responsible for a maternal death*

(b) Fetal Abortions, miscarriages and stillbirths remain higher in diabetic than nondiabetic pregnancies Furthermore, the fetal and neonatal mortality have been found to be as high during the five years preceding the onset of diabetes as after the disease developed[3] White[4] has reported a fetal survival rate of 82 per cent in 433 consecutive diabetic pregnancies, but this varied with the occurrence of normal* or abnormal balance of sex hormones If the sex hormones were normal the fetal survival was 95 per cent, if abnormal and uncorrected, the survival rate was only 58 per cent, if abnormal but corrected with estrogen and progesterone therapy, the survival rate rose to 89 per cent In seventy eight fetal deaths (18 per cent) there were hormonal imbalances in 97 per cent of the mothers 66 per cent of the mothers had onset of diabetes before they were ten years of age,

* Serum chorionic gonadotropin values not in excess of 200 rat units per 100 cc

52 per cent had had diabetes for more than ten years, 46 per cent had hypertension or albuminuria, 33 per cent had arteriosclerosis (20 per cent had arteriosclerotic changes in the pelvic vessels as detected by roentgen ray examination, Fig 29), 5 per cent had been in diabetic coma during the pregnancy and 1 per cent in eclampsia

**The Diagnosis of Diabetes Complicated by Pregnancy.** When a pregnant woman develops diabetes, the diagnosis of this disease may be complicated because of the great frequency with which renal glycosuria occurs in normal pregnant women The diagnosis of renal glycosuria as opposed to that of diabetes can be established by simultaneous determinations of the sugar in the blood and urine (see p 88) In questionable cases, glucose tolerance tests are indicated A pregnant woman showing glycosuria, even with a normal glucose tolerance curve, but having a family history of diabetes, should be watched for the development of diabetes for several years

**The Effect of Pregnancy on the Diabetes.** The effect of pregnancy on the diabetes is unpredictable In some, the insulin requirement remains unchanged, in others it decreases, and in still others it increases.

*In general, and if the diabetes is well controlled, we have found the need for insulin (a) to increase slightly during the first trimester—probably a reaction to endocrine readjustments, (b) to remain relatively stationary in the second trimester—the qualitative development phase for the child, and (c) to be increased in the third trimester—during the phase of quantitative growth with an overall increase in the total metabolism*

Occasionally the mother's diabetes appears to improve in the last trimester It is probable that this is due to insulin provided by the fetus because, following delivery, the insulin need in these cases increases. Much more common is the steady increase in the insulin requirement during the last three months of pregnancy This is an expected response to the increase in total metabolism accompanying the increase in the size of the baby.

Diabetes is not made worse by pregnancy if it is adequately controlled during the period of gestation

**Management of the Pregnant Diabetic Patient.** *General Measures* The regimen is, in general, the same for the pregnant diabetic woman as for the non pregnant Good general hygiene and a reasonable amount of outdoor exercise are encouraged The patient must be under close scrutiny by both the internist and the obstetrician throughout the pregnancy. She should be seen every two weeks during the first two trimesters, and every week during the last trimester

*Diet* In general, the diet should be adequate to prevent undernutrition during pregnancy and, as there is considerable evidence that diabetic patients need more vitamins than is usually the case, special care is taken to prevent vitamin deficiencies

TOTAL CALORIES These are calculated as for the nondiabetic (p 105)—

multiply the ideal body weight (see Appendix) in pounds by 10 and in case of pregnancy add 100 calories The correction for activity will be varied according to the behavior of the body weight but for the initial diet 30 per cent of the basal diet *is added* *Example* *Patient twenty eight years* of age, ideal weight 136 pounds

| | |
|---|---|
| Multiply ideal weight by 10 (136 × 10) | 1360 |
| Correction for age and pregnancy add | 100 |
| Basal calories | 1460 |
| Add 30 per cent for activity | 438 |
| Total calories | 1898 |

PROTEIN *Multiply the ideal weight in pounds by ⅞ to determine the protein in grams* In the illustrative case above this would be ⅞ × 136 = 119 gm

CARBOHYDRATE We prefer a liberal quota of carbohydrate, e g, *250 grams or more* *The calories not provided by protein and carbohydrate* are supplied by fat, e g,

| | |
|---|---|
| Protein 119 × 4 | 476 calories |
| Carbohydrate 250 × 4 | 1000 calories |
| Calories from protein and carbohydrate | 1476 |
| Fat = 1898 − 1476 = 422 422 − 9 = 47 gm | |

DIETARY SUPPLEMENTS One quart of milk, or skim milk, is included in each day's diet to care for the need for calcium Also, in view of evidences that diabetic patients may need more vitamins than nondiabetics, supplementary vitamins* are prescribed

There is considerable latitude in the need for vitamins during pregnancy The following amounts are regularly prescribed for daily use

| | |
|---|---|
| *Vitamin A* | 6000 I U |
| *Vitamin D* | 400 to 800 I U |
| *Vitamin B Complex* | Thiamine HCl 1 8 mg |
| | Riboflavin 2 5 mg |
| | Nicotinic acid 18 mg |
| *Vitamin C* | 100 mg |
| *Vitamin K* | 2 mg of synthetic vitamin K, intramuscularly at least four hours before delivery or preferably 2 mg daily for each of two days before delivery |

*Insulin* We give insulin to every pregnant diabetic patient The amount, brand and distribution are determined as for the non pregnant patient but special care is taken to keep the fasting and postprandial blood sugar values within normal ranges This may require one to three injections of insulin daily

In cases in which the insulin requirement increases steadily during the

* One therapeutic vitamin capsule (Squibb) on alternate days will provide adequate amounts of vitamins A D thiamine HCl, riboflavin niacinamide and ascorbic acid The supplemental administration of vitamins E and K has been recommended

final trimester—the usual occurrence—a marked reduction in the need for insulin follows delivery Contrariwise, when the severity of the diabetes appears to be greatly alleviated and the need for insulin decreases during the last three months of gestation delivery is followed by an increased severity of the diabetes and insulin must be given in increased amounts to control the diabetes and to avert ketosis (Duncan and Fetter) [3]

**The Management of Complications.** *Nausea and Vomiting* The nausea and vomiting of pregnancy has rarely been troublesome in our experience with these patients Frequent feedings supplemented by glucose administered intravenously may be necessary to prevent ketosis In this event a temporary schedule of four, or six, feedings in each twenty four hours with regular insulin before each is employed as in dealing with other acute complications (see p 217) This program is usually not needed but when it is the normal or usual regimen is restored as promptly as is practicable

*Correction of Hormonal Imbalance* The relative merits of hormonal therapy, high protein diets with supplements and early delivery by cesarean section are not clear Nevertheless, the combination of all three has afforded the best therapy to date for these patients and it is recommended for use until more effective measures are available and proven

In White's[4] series of 439 cases, only 17 had a normal hormonal balance and therefore did not need substitution treatment A severe diabetes of long standing favors the development of hormonal imbalance, which appears to be a faulty production of progesterone with poor production, or metabolism, of estrogens and compensatory high levels of serum chorionic gonadotropin—above 200 rat units per 100 cc Unfortunately, the laboratory procedures necessary for the detection of a hormonal imbalance, viz., serum level of estrogen and chorionic gonadotropin, and urinary excretion of pregnandiol, are expensive and not available in most laboratories Furthermore, the cost of the estrogen (diethylstilbestrol) and progesterone (proluton) in the doses recommended is often prohibitive

Hormonal determinations—serum gonadotropin and quantitative excretion of estrogen and pregnandiol—should be made, if possible, in all pregnant diabetic women, and corrected if an imbalance is found If the determinations cannot be made, we advise substitution therapy in all pregnant women with long standing or severe diabetes, and in patients with a history of a previous obstetrical accident

*Estrogenic hormone is given to prevent the elevation of serum chorionic* gonadotropin, and progesterone is given to prevent excessive destruction of estrogen

The hormonal therapy recommended by White[4] entails the daily intramuscular injections of estrogen (diethylstilbestrol) and progesterone (proluton) according to the schedule outlined in Table 33

ORAL ADMINISTRATION OF DIETHYLSTILBESTROL. A less expensive therapy has been recommended by Smith,[5] comprising the oral administration of

## TABLE 38

### Hormonal Therapy According to Clinical Classification of Pregnant Diabetic Women[4]

**I CLINICAL CLASSIFICATION**

| | A | B | C | D | E | F |
|---|---|---|---|---|---|---|
| | 1 Mild diabetes<br>2 No insulin<br>3 Little dietary regulation needed<br>(5% of series) | 1 Diabetes onset after 20 years of age and<br>2 Of less than 10 years' duration<br>3 Free of vascular disease<br>(29% of series) | 1 Diabetes for more than 10 years<br>2 Onset between 10 and 19 years of age or those with minimal vascular disease<br>(44% of series) | 1 Diabetes for 20 years or more<br>2 Onset under 10 years of age or considerable evidence of vascular disease<br>(14% of series) | Calcified pelvic arteries<br>(7% of series) | All patients with nephritis<br>(1% of series) |

**II SUBSTITUTION THERAPY**
Diethylstilbestrol and Proluton in Mg per day

| Week of Pregnancy | A | B–C | D | E–F |
|---|---|---|---|---|
| 9–16 | 0 | 5 | 10 | 25 |
| 20–23 | 0 | 10 | 15 | 50 |
| 24–27 | 0 | 15 | 25 | 75 |
| 28–31 | 0 | 25 | 50 | 100 |
| 32 and up | 0 | 50 | 75 | 125 |

diethylstilbestrol in doses of (a) 5 mg daily, by mouth, beginning during the sixth or seventh week of pregnancy (*counting from the onset of the last menses*), (b) the daily dose is increased by 5 mg at two week intervals to the fifteenth week (c) 25 mg daily in the fifteenth week (d) Thereafter the daily dose is increased by 5 mg at weekly intervals (e) Diethyl stilbestrol is discontinued at the end of the thirty fifth week

Treatment is begun not later than the sixteenth to the nineteenth week and the initial dosage is always the one for the particular week of pregnancy according to the plan of therapy outlined above

*Salt Restriction* A moderate restriction of the daily salt intake, not more than a total of 3 gm if edema is present and even greater restrictions are exercised if the retention of salt and water assumes more than a mild degree In addition, courses of *ammonium chloride*—4 to 8 gm daily for three days—are given as needed with rest periods of two or three days between courses

*Termination of Pregnancy* The choice between permitting spontaneous delivery and delivery by cesarean section is not always an easy one Barring obstetrical contraindications we prefer spontaneous deliveries when

(a) the mother has had a previous and successful confinement, and

(b) when the diabetes is of recent onset and there is a normal concentration of chorionic gonadotropin in the serum and with no signs of toxemia

Following White s lead, cesarean section early in the thirty eighth week is recommended for

(a) primiparae

(b) pre eclamptic patients with increasing blood pressure, edema and albuminuria

(c) those in whom the chorionic gonadotropin has not been reduced to normal

(d) those who have had previous abortions or stillbirths and no successful full term pregnancies, and

(e) if the baby appears to be unusually large

The risk attending a cesarean section is extremely small Furthermore, the management of the diabetes is subjected to less disturbance by this method of terminating the pregnancy than if normal labor is permitted

These rules almost identical to those advocated by White, simplify the problems surrounding the termination of pregnancy and have led to gratifying results

*Treatment During Labor and Delivery* The patient is given the equivalent of 10 to 15 gm of carbohydrate per hour during labor, which amounts to 150 to 200 gm if the labor is long The carbohydrate is given by mouth if practicable Otherwise it is administered intravenously as 10 per cent dextrose in normal saline solution or distilled water Regular insulin is

given in small doses at four hour intervals, the amount being increased or decreased according to whether sugar is present or absent in each specimen of urine Exact control of the diabetes is not important for the short period involved The aim is to prevent (a) ketosis and (b) hypoglycemia

*Anesthesia* Ordinarily, caudal anesthesia is employed for spontaneous vaginal deliveries and spinal anesthesia for delivery by cesarean section

*Treatment During the Early Postpartum Period* A prompt reduction in the insulin requirement occurs in most patients after delivery, and especially in those whose insulin requirement increased in the final trimester of pregnancy Obese patients who required large amounts of insulin during pregnancy can usually get along without it within a few days after delivery

*Lactation* Diabetic women lactate poorly even though the diet is ample Supplementary feedings are needed if the mother nurses her baby, a procedure which is not advocated for diabetic mothers The deficiency of milk may be due to a decrease in the lactogenic hormone of the anterior pituitary gland The diabetic mother who nurses her baby needs less insulin than she did before she became pregnant Since lactose in the urine may be mistaken for glucose, and since the lochia renders the urine unsuitable for examination during the early postpartum period, frequent blood sugar determinations are needed to guide the insulin dosage in the lactating mother

*Postpartum Complications* Eclampsia may develop in the postpartum period It is treated, if it occurs, as in the nondiabetic, with intravenous injections of dextrose solution and of concentrated human albumen (salt free), oxygen therapy, intramuscular injections of 50 per cent magnesium sulfate solution and sedatives Pyelitis and pyelonephritis are the most common causes of postpartum fever in the diabetic patient Sulfonamides or streptomycin are indicated as in the nondiabetic (see p 193) Puerperal fever, a rare combination, is also treated as in the nondiabetic While infection persists the insulin dosage is increased as need be and the patient should be placed on the regimen for patients with acute complications (see p 214)

**Care of the Newborn Infant of the Diabetic Mother** The infant *born to a diabetic mother needs special* care The chief dangers of the neonatal period are hypoglycemia and asphyxia Compensatory overactivity of the fetal pancreas with resultant hypoglycemia in the infant is doubtless the result of inadequate control of the mother's diabetes during the last *trimester of pregnancy Exact control of the mother's diabetes during ges*tation tends to prevent hypoglycemic attacks in the newborn infant It is wise to give the infant feedings of a 5 per cent aqueous solution of lactose, through a medicine dropper, every two hours from birth through the first three days of life *The use of lactose water obviates the need for intra*muscular or subcutaneous injections of dextrose solution

Respiratory difficulties, with a tendency to asphyxia, occur more often

in infants born of diabetic than of normal mothers. Ketosis, hypoglycemia, or trauma to the cerebral cortex from a long labor associated with a large baby may contribute to the production of asphyxia. In White's series, 60 per cent of the infants showed some degree of respiratory difficulty. Special care in removing mucus from the infant's mouth and throat by suction and postural drainage, and the use of an incubator, in which the temperature is 29° C. (84.2° F.) and the atmosphere contains a large amount of oxygen, will reduce the danger of asphyxia.

*Fetal Anomalies.* Congenital defects are unduly frequent in babies born of diabetic mothers. White reported that twenty-two of 125 babies born to diabetic women had twenty-six congenital defects. Thus one [illegible] defect, compared to one in fifty [illegible] congen[illegible] [illegible] imb[illegible]

*L*[illegible] born *to diabetic mothers are often unusually large.* In 125 pregnancies, White found that 80 per cent of the infants exceeded the normal weight. The length of these babies, as well as the weight, exceeded normal. The overweight was considered to be due to *fat, edema** and *splanchnomegaly*, the latter being most marked in the liver, spleen and heart. Microscopic evidence of *hematopoiesis* of the spleen and liver was seen in fourteen of the seventeen infants upon whom autopsies were performed. Atelectasis was observed in thirteen, persistence of fetal glomeruli in six, and hyperplasia of the islets of Langerhans in five. These infants showed the general appearance of postmaturity: long hair, double eyelashes, atelectasis, and enlargement of the spleen. Miller and Wilson[7] have likewise reported cardiac hypertrophy, excessive erythropoiesis in the liver, and hyperplasia of the islets of Langerhans in babies born to diabetic mothers. These findings were most frequent in the large babies.

**Outlook for the Child.** If the infant of the diabetic mother is born alive, its chances of survival are nearly as good as those of infants born of normal mothers, and the mortality during the first year of life of babies born of diabetic mothers is the same—5 per cent—as that for babies born of nondiabetic mothers (White).

Diabetes is transmitted as a recessive Mendelian trait. Hence the child cannot inherit the disease from the mother alone. Unless the father has diabetes also, or carries a recessive factor for diabetes, the child will not develop the disease.

**Summary.** *Although good control of the diabetes in the pregnant woman has reduced the maternal mortality to almost nil, the incidence of abortions, miscarriages and stillbirths remains much higher than in non-diabetic women. This high fetal mortality is due to the high incidence of* toxemia in diabetic women, which in turn results from the high incidence

* Edema of the newborn infants of diabetic mothers is mentioned in medical writings as a common occurrence. It has not been a common complication in our cases.

of vascular disease and the frequent imbalance of sex hormones The latter can be successfully treated with estrogenic hormone and progesterone, but so far the problem of vascular disease in long standing diabetes has not been solved During pregnancy, there is an increase in the insulin requirement, especially in the first and third trimesters, and after delivery the insulin requirement usually decreases rapidly With adequate control of the maternal diabetes during the last trimester, overactivity of the islets of Langerhans of the fetal pancreas is probably prevented, and the risk of hypoglycemia in the newborn baby thereby decreased We favor normal spontaneous delivery in diabetic women, unless an indication for cesarean section aside from the diabetes exists The newborn infant of the diabetic mother needs special care to prevent the development of hypoglycemia and asphyxia

## REFERENCES

1 White P Proc Am Diabetes A 6 259 1946

CHAPTER XIX

# The Diabetic Child

## INTRODUCTION—INCIDENCE—SPECIAL RISKS

The child with diabetes poses problems which are often more complicated than those presented by the adult diabetic. Relatively, the child is in a state of metabolic and psychologic instability. He is subject to changes that accompany growth, to fluctuations in metabolic and emotional patterns and to the inability of the immature mind to comprehend the problems which diabetes presents.

Diabetes is uncommon in children. One child in two thousand under the age of fifteen, regardless of sex, may be expected to develop diabetes. The incidence is slightly higher in the Jewish segment of the population.

A prompt diagnosis followed by adequate treatment eliminates mortality due to diabetes in children. However, undiagnosed and passing as "nephritis," "bed wetting" or a "behavior problem," diabetes in children may be complicated by a ketosis with great rapidity. But, even at this stage, if the maladies—diabetes and ketosis—are identified, prompt therapy, though more complicated, is successful in restoring good health.

## ETIOLOGY

The influence of heredity in the development of diabetes is established. An heredity factor is the outstanding and possibly the only common predisposition to diabetes in childhood. Unlike in the adult, obesity plays no apparent part in precipitating diabetes. A clear cut history of diabetes in the family is not always obtained. There are obvious reasons why this should be, but one important one is that the parent, or parents, may not develop clinical diabetes until long after the child has been under treatment for this disease. Future families having diabetes, the almost simultaneous development of diabetes in twins and family trees spotted with diabetes are inescapable evidences of the influence which heredity exerts. Furthermore, the studies of Pincus and White[1] have shown that the development of diabetes follows a Mendelian pattern and with recessive characteristics.

Overactivity of endocrine glands has a less secure place as an etiologic factor in precipitating diabetes. However, children are taller than normal

at the onset of the disease Also, these children exhibit bone development in advance of their ages and secondary sexual characteristics develop prematurely, and ketosteroid excretion values tend to be higher than in non diabetic children of the same age To blame the pituitary gland is inviting and it is highly probable that this gland plays a part, even if not the predisposing part, in producing clinical diabetes

There is no evidence that *infection causes diabetes*

## SYMPTOMS

*The symptoms* of diabetes in children are more sudden in onset and more marked in their severity than in the adult Cases with an insidious onset do occur but they are uncommon We have seen one such patient who had been treated for "nephritis" for four months because of nocturia!

In the infant, who cannot make his complaints known, the possibility of diabetes should be kept in mind when thirst and weight loss are marked Older children may complain of being tired, an inability to 'keep up," aching in the extremities, and headache Excessive thirst, hunger, frequency of *urination and loss of weight are the most consistent group of* symptoms Loss of weight, in child or adult, in the presence of an increased ingestion of food, is suggestive of diabetes mellitus, although the other *causes of loss of weight, notably intestinal and nutritional disorders and* overactivity, are not to be disregarded Occasionally, the diabetic child is in coma due to ketosis when first seen by a physician This is particularly true when some other complication, notably an acute infection, may attract the parents' attention and at the same time intensify the speed with which ketosis develops In such cases diabetes may even escape the physician's attention if he does not make a routine practice of examining the urine In these cases the excessive appetite gives way to anorexia, nausea, and often vomiting extreme degrees of lassitude and somnolence The frequent passing of large quantities of urine is an invariable symptom and continues well into the ketotic phase and until the dehydration is of such a *degree that it tends to reduce the amount of urine produced*

## DIAGNOSIS

The acuteness of diabetes in *childhood* increases *the likelihood of a* prompt examination, the polyuria attracts attention to the urinary tract, and glycosuria is found The renal threshold for sugar is not elevated in children and if the urine is examined during the course of symptoms sugar will almost invariably, be found Specimens voided two to three hours

Glycosuria having been found, the diagnosis is [illegible] tration of sugar in a sample of venous blood taken before breakfast exceeds 130 mg per 100 cc, or if in excess of 160 mg per 100 cc if the blood is

taken after a normal meal If there is doubt about the diagnosis, a test meal (see p 79) may be given, and if the diagnosis is still not clear a glucose tolerance test (see p 82) is done, giving 1 75 gm of glucose per kilogram of the normal body weight The spacing of the blood sugar determinations and the interpretation of the test are the same as for the adult (see p 82)

## PREVENTION

There is no known practicable means of preventing diabetes in children To be successful in preventing diabetes, diabetics and persons predisposed to diabetes by heredity would need to marry into nondiabetic families This impracticable plan, if continued for several generations would tend to delete diabetes There is no convincing evidence that diet restrictions or additions play any part in preventing diabetes in children

## TREATMENT

The successful treatment of the juvenile diabetic entails a special understanding of the disease process in the child and an appreciation of his attitude towards the disease, towards treatment, towards his playmates and towards life

The success of therapy will depend largely on the ability of the physician to secure the confidence of the child Special needs for the growing and developing child—the physical and mental needs—are to be considered Furthermore, the regimen should be as flexible as is practicable and should be shaped in such a way that a reasonably normal life and normal childhood activities are possible The criteria of good control for a diabetic child are

1 Adequate nourishment.
2 A fasting blood sugar level below 150 mg per 100 cc and postprandial levels below 200 mg per 100 cc
3 Freedom from "major" or consistent glycosuria
4 Cholesterol content of the blood below 230 mg per 100 cc
5 Normal physiologic and psychologic adjustment and development

Our practice has been to admit all new diabetic children to the hospital for a period of standardization and training Under ordinary circumstances this is the wisest procedure However, if adequate facilities for metabolic studies and instructions in diet and insulin therapies are available in the out patient service or physician's office, there may be certain advantages to providing the instruction with the patient carrying on his normal activities The child learns to live with his disease in his home environment and the problems of management can be solved as they arise This prevents the necessity for a second period of adjustment after discharge from the hospital. During this period frequent visits to the office are necessary—as often as three or more visits per week—for the first few weeks This is

at the onset of the disease Also, these children exhibit bone development in advance of their ages and secondary sexual characteristics develop prematurely, and ketosteroid excretion values tend to be higher than in non diabetic children of the same age To blame the pituitary gland is inviting and it is highly probable that this gland plays a part, even if not the predisposing part, *in producing clinical diabetes*

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essential not only in the solution of problems as they arise but also because there is a marked tendency for a reduction in the insulin requirement to occur during the first two weeks of adequate management Close checks on the blood sugar levels and glycosuria at frequent intervals are advisable in order to anticipate and prevent hypoglycemic reactions

**Diet** Unlike the adult the child is constantly adding to the size of his body Adequate dietary provisions are taken into consideration for this continuing and variable growth Special attention is given to the protein content of the diet and to the total calories as requisites for normal development Carbohydrate is scarcely less important as a source of energy Fat is chiefly important as a source of calories

TABLE 39

Energy Requirements of Children*

Total Calories for Children According to Body Weight

| AGE IN YEARS | CALORIES PER KILOGRAM | | CALORIES PER POUND | |
|---|---|---|---|---|
| 1– 2 | 100–90 | | 50 45 | |
| 3 5 | 90–80 | | 40 36 | |
| 6– 9 | 80–70 | | 36 32 | |
| 10 13 | 70–60 | | 32 27 | |
| | Boys | Girls | Boys | Girls |
| 14 15 | 60–55 | 50–45 | 27 25 | 23 20 |
| 16 17 | 60–55 | 45–40 | 27–25 | 20–18 |
| 18 19 | 55–50 | 40 35 | 25 23 | 18 16 |

* Rose *Foundation of Nutrition* The Macmillan Company 1933

*Calories* The child, because of his great expenditure of energy, his needs for growth and his relative increased surface area per unit of body weight, needs more calories per kilogram than those who are fully grown The very high requirements of infancy and early childhood fall gradually until after puberty, they reach the adult levels These considerations are indicated in Table 39

*Protein* Protein is "construction material"—an essential for growth Modern dietetic practice is tending toward more generous allowances of protein for adults as well as for children and there are reasons to believe that this will lead to better development, better health and increased longevity

*The daily protein allowances for children are from a minimum of 2 0 gm per kilogram of the normal weight to 3 0 gm per kilogram* (0 9 to 1 1 gm per pound) Larger quantities of protein are permissible during the correction of malnutrition and patients with a "labile diabetes" are less likely to have hypoglycemic reactions if the protein content of their diets

is high Presumably this benefit derives from the slow delivery of carbohydrate from protein foods

*Carbohydrate* All diabetic children need insulin Hence there need be no severe restriction of the carbohydrate quota when, for a few more units of insulin, nearly normal amounts of carbohydrate are well tolerated

*The maximum daily carbohydrate allowance is 320 gm Until this maximum is reached we prescribe 50 per cent of the total calories as carbohydrate*

The distribution of the carbohydrate in the diet for the child is the same as for the adult (see p 103) It is always permissible to save part of any meal for consumption two or three hours later Regularity of the quantitative distribution of carbohydrate from day to day is an important feature in preventing needless risks of hypoglycemia, or of extreme degrees of hyperglycemia

Ordinarily diabetic patients are advised not to eat sugar, the reasons being that it is a very concentrated food, devoid of vitamins and minerals, and takes the place of bulkier foods containing both of these accessory food factors However, we have no objection to the use of cane sugar in small and appropriate amounts when it is desirable to reduce the bulk of the diet and provided precautions are taken against the development of mineral and vitamin deficiencies

*Fat.* Fats are important as sources of calories, fat soluble vitamins, essential fatty acids, and as a great addition to the palatability of the diet The diabetic child has a tendency to hypercholesterolemia and an excess of fat in the diet may accentuate this trend Approximately 20 per cent of the total caloric content of the diet is in the form of fat and the main sources are dairy products, margarine and meat If the hypercholesterolemia is marked and persistent, even after the institution of insulin therapy, the amount of fat is reduced in favor of a more liberal carbohydrate quota and the fatty portions of meats, which are high in cholesterol, are eliminated

*Minerals* The demands for minerals are high in the growing child Infants need 6 mg of iron per day and the need increases to 20 mg daily during periods of maximum rate of increase in weight Adequate amounts of calcium and phosphorus will be supplied by one quart of whole milk daily in addition to the other dietary constituents

*Vitamins* If the protein, fat and carbohydrate needs of the child are met from natural foods, well prepared, and containing liberal amounts of milk and raw fruit and vegetables, there need be no concern about the possibility of vitamin deficiencies However, methods of preparation, seasonal variations in the quality of foods, and the availability of simple complete vitamin supplements have led us to employ routinely a multiple vitamin supplement capsule daily in the treatment of children with diabetes

**Insulin.** All diabetic children need insulin therapy Practically all dia

betic children succumbed within two years to the disease in the pre insulin eras In general the principles governing insulin therapy are the same for the child as for the adult The criteria for good control and the speed and duration of insulin action are the same However, there are relatively stable homeostatic mechanisms which tend to provide *a wide margin of* safety between a hypoglycemia and a hyperglycemia in most adult diabetics which are not nearly so efficient in the child As a result the concentration of sugar in the blood of a child diabetic is much more labile and may change rapidly from a high level to a low one or vice versa Furthermore these changes are set in motion by conditions which in the adult would have little effect, e g, a change of 2 or 4 units of insulin, physical exercise and delayed meals In fact, all influences which tend to change the insulin requirement (see p 43) tend to have a more intensive effect on the child than on the adult

Some adult patients have diabetes that has the labile* characteristics of diabetes in the child

The small margin of safety between hypo and hyperglycemia in the child is doubtless related to the smaller supply of glycogen on one hand and to the amount of physical exercise indulged in on the other It is because of this narrow margin of safety that mild degrees of glycosuria are considered advisable as indications of security against hypoglycemic reactions The amount of glycosuria need not exceed 10 gm daily if there is appropriate timing of the meals and insulin as illustrated on pages 108 to 111

The selection of the insulin regimen is much the same as that for the adult. In practically no case does a single dose of protamine zinc insulin control the diabetes satisfactorily A single dose of globin insulin is satisfactory in a small number of cases A mixture of protamine zinc insulin and regular insulin 2 1 or occasionally 3 1, is more effective than a single dose of either protamine zinc insulin or globin insulin One relatively large dose of globin insulin one hour before breakfast and a very small dose before supper is satisfactory in some cases A mixture of protamine zinc insulin and regular insulin 2 1 (or 3 1) fifteen minutes before breakfast and a small dose of regular insulin before supper is a most effective plan of therapy

*However, very good results have been secured with a mixture of* NPH [illegible] *tes before*

[illegible] diabetic patient (see p 108)

Checking the control of the diabetes is effectively done by securing on the test day—usually within a day or two before discharge from the hos

* These cases of labile diabetes are often referred to as brittle diabetes"—a poor term.

pital—a blood sugar value before breakfast and one at 3 P M , and by testing a specimen of urine voided before each meal and at bedtime for sugar

The fasting blood sugar value is an index of the adequacy of the previous day's dose of protamine zinc insulin, the 3 P M value will indicate the effectiveness of the morning dose of globin insulin The presence or absence of glycosuria just before lunch is a check on the morning dose of regular insulin, the results of testing the urine voided before supper and at bedtime are further checks on the effect of the morning dose of globin or NPH insulin

Determination of the sugar values of blood withdrawn before each meal and at bedtime provides a more critical check which is used occasionally

The results of the foregoing tests not only indicate the degree of control of the diabetes but may indicate a change of the type of insulin or a different distribution or a mixture may be suggested

The needs of the child diabetic are more subject to change than those of the adult *Each office visit should be the occasion for checking the blood sugar, fractional urinalyses, body weight, rate of growth* (Fig 32), *physical activities and general health*

Home reports are kept by the patient when practicable, or by a parent when necessary One testing of the urine daily is desirable and a test before each meal and at bedtime is done one day per week The latter method is adopted daily in the event of any complicating illness or if the tests reveal large amounts of glycosuria The results serve as an index upon which to base a change of insulin or diet, or both

**Exercise.** The importance of normal exercise in the physical, mental and social development of a child is great and the diabetic child should not be excluded from these activities The modern treatment for diabetes makes it possible for the child to fit into group or individual athletics in a normal manner One of our patients was a star performer on his high school swimming team, another is an enthusiastic tackle on the 80-pound squad A nationally famous tennis player has a severe grade of diabetes

Physical exertion reduces the blood sugar in addition to, and independent of, the insulin activity in operation at the time Violent physical exertion is therefore likely to produce a hypoglycemia unless an adequate adjustment in diet or insulin, or both, is made in advance Since there is no appreciable harm to be expected from a transitory hyperglycemia it is our practice to supply an excess of readily available glucose by mouth just before the exercise is begun An apple or a banana is not only permissible but desirable A candy bar is even permissible before a strenuous game or a long hike A short period of hyperglycemia is to be preferred to the risk of an insulin reaction This precautionary measure is particularly important prior to swimming where the exercise may be prolonged and where the apparent danger from a hypoglycemia is increased

**Education.** These children are usually intellectual beyond their years

betic children succumbed within two years to the disease in the pre insulin eras In general, the principles governing insulin therapy are the same for the child as for the adult The criteria for good control and the speed and duration of insulin action are the same However, there are relatively stable homeostatic mechanisms which tend to provide a wide margin of safety between a hypoglycemia and a hyperglycemia in most adult diabetics which are not nearly so efficient in the child As a result, the concentration of sugar in the blood of a child diabetic is much more labile and may change rapidly from a high level *to a low one or vice versa Furthermore* these changes are set in motion by conditions which in the adult would have little effect, e g , a change of 2 or 4 units of insulin, physical exercise and delayed meals In fact, all influences which tend to change the insulin re quirement (see p 43) tend to have a more intensive effect on the child than on the adult

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*The distribution of the diet is identical with that for the adult diabetic* patient (see p 108)

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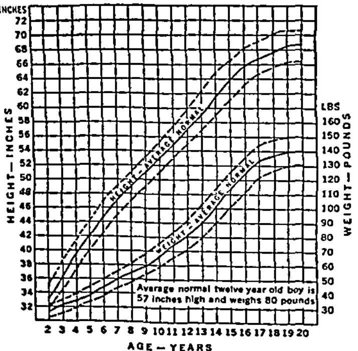
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**Exercise** The importance of normal exercise in the physical, mental and social development of a child is great and the diabetic child should not be excluded from these activities. The modern treatment for diabetes makes it possible for the child to fit into group or individual athletics in a normal manner. One of our patients was a star performer on his high school swimming team, another is an enthusiastic tackle on the 80-pound squad. A nationally famous tennis player has a severe grade of diabetes

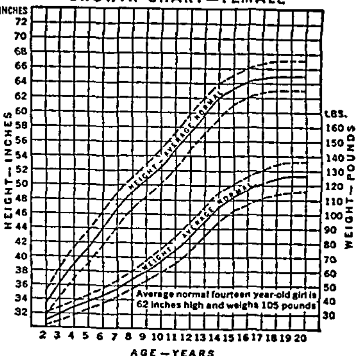
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[illegible] a long hike. A short period of hyperglycemia is to be preferred to the risk of an insulin reaction. This precautionary measure is particularly important prior to swimming, where the exercise may be prolonged and where the apparent danger from a hypoglycemia is increased

**Education** These children are usually intellectual beyond their years




Solid lines indicate average normals, broken lines, 10 percent above or below ideal normals




Solid lines indicate average normals, broken lines, 10 percent above or below ideal normals

Fig 32 Normal growth patterns. (Presented through the courtesy of Dr J H Barach.)

and frequently their understanding is better than that of adults Their limitations should be stressed only enough to lead them to take sensible precautions Thus the circumstances under which hypoglycemia may develop (exercise or delayed meals) should be explained and adequate preventive measures described The reason for insulin and the dangers of omitting a dose are pointed out By the age of eight or ten years the child should be giving himself the insulin injection and should be capable of performing the urinalyses required The Clinitest method of testing for sugar is simple and can be performed at an early age Familiarity with the food exchanges and a knowledge of the flexibility they permit give the young as well as the older patient great reassurance

As the child matures it is well to guide him, if possible, into an occupation not requiring contact with power-driven machinery or irregular hours of dining or sleeping. The use of tobacco should be discouraged since there are many reasons to believe that this habit may accentuate the vascular troubles that so frequently develop in adult life

Reassurance, commenting on favorable progress at school and in sports are valuable in developing and increasing a will to follow the pattern of living which will not be completely normal but will afford, to these young patients, opportunities to excel which would otherwise be denied

**Special Considerations.** With control of the diabetes there tends to be a decline in the insulin requirement during the first few weeks Thereafter, as the child grows the general tendency is for the insulin requirement to increase, more or less in proportion to the increase in size of the body

In some girls there may be a tendency to hypoglycemia just before the menstrual period In others the opposite is true Usually these tendencies will be quantitatively consistent from month to month so that provisions can be made by altering the dose of insulin at the appropriate time

As the child grows his requirements for food as well as for insulin, gradually change and the diet should be reviewed at intervals of not longer than six months, in the light of changes in weight and age As adolescence is passed the diet should be based on adult requirements

All of these children should wear engraved medal identification bracelets A suitable inscription might be

Front I take insulin If I am sick or faint give me sugar Call a doctor (over)

Back Name and address

The education, training and adjustment of the diabetic child can be expedited by a summer or two at a camp for diabetic children Many of these camps, with adequate medical and educational personnel, are coming into existence Here the child by being with other diabetic individuals, loses his sense of being handicapped He is taught that he can live with, and make light of his extra load The stimulus to becoming self-sufficient is great under these conditions and a fretful, resentful child frequently be-

comes proud of his ability to cope with his disease Every child with diabetes, who is otherwise healthy, should be given an opportunity to attend a diabetic camp

## COMPLICATIONS

**Ketosis** Children suffering from diabetes are, generally speaking more prone to develop ketosis than are adults This is because of (1) the labile character of their disease, (2) the greater variety of circumstances which will upset their regimen, (3) the greater frequency of intercurrent febrile diseases, and (4) fluctuating severity of the diabetes itself

The more common precipitating causes of diabetic coma are

(a) Infections causing loss of appetite—added to this, the insulin may be erroneously omitted A dose of insulin is never to be omitted while glycosuria is present If a patient cannot take food, one half of his usual dose of insulin is taken and a small amount is taken every four hours until seen by a physician, if strong reactions for glycosuria prevail The management of the diabetes during acute complications is the same for the child as for the adult (see p 212)

(b) Errors in the dosage or the complete omission of insulin

A word of caution is sounded regarding abdominal pain in the juvenile diabetic This symptom is frequently encountered in cases of ketosis in child diabetes Abdominal pain, vomiting splinting of the abdominal muscles and leukocytosis mimicking an acute appendicitis in detail are promptly corrected if due to ketosis by relieving a distended stomach and by administering sodium chloride If relief is not prompt the possibility of an acute surgical condition is greatly enhanced

**Surgical Complications** The management of the diabetes during surgical complications is the same for the child as for the adult (see p 221)

### *Miscellaneous Considerations*

1 **Diabetic or Pseudodwarfism** Uncontrolled and severe diabetes in early childhood causes a stunting of physical growth—a pseudodwarfism Growth, sexual and osseous development are retarded The abdomen is protuberant and there is enlargement of the liver Obesity frequently develops after the diabetes is controlled

The cause of this pseudodwarfism is not known Malnutrition, secondary to the diabetes is doubtless an important factor Hypogonadism is indicated by the reduced excretion of ketosteroids but there are evidences of activity of the anterior pituitary gland and the basal metabolic rate tends to be elevated Nevertheless a decrease in the growth hormone is a probability

*Treatment* Control of the diabetes and more liberal quotas of protein than are usually prescribed are advisable Supplementary vitamins are given and thyroid therapy is tried very cautiously It is doubtful if the benefit observed is actually due to the thyroid medication

White reports good results from the intramuscular injections of pituitary extracts so long as the epiphyses are open but that after seventeen years of age puberty is precipitated with therapy but physical dwarfism remains. Testosterone propionate* causes accelerated growth in retarded boys.

2 **Hepatomegaly.** Enlargement of the liver is uncommon when the diabetes has been well controlled. The liver may be quite large, extending into the pelvis, and its edge is firm, sharp and slightly tender. The enlargement is due to excessive deposits of glycogen, or fat, or to hydropic degeneration. The function of the liver is not grossly impaired. The liver usually reverts to normal size following a short period of good control of the diabetes, but this transition is accelerated by administering lipotropic substances. Our experience is chiefly with choline in doses of 2 gm three times daily.

3 **Premature Degenerative Changes.** The incidence of degenerative disease in adults who have had diabetes since childhood is extraordinarily high. Premature *arteriosclerosis* is the most common of these changes, though the incidences of *retinitis* and of *renal disease* are also higher than in those who acquired diabetes after childhood.

*Juvenile cataracts*, though rare, develop with great speed and always in those children with poorly controlled diabetes. The opacity involves the anterior and posterior portions of the optic lens and leads to great impairment in vision. The treatment depends on the stage of development of the disorder when detected. Control of the diabetes may halt its progress, "needling" of the lens may be effective, or surgical removal may be necessary.

So far, the only preventive measures that offer optimistic results against the foregoing degenerative disorders are (a) control of the diabetes and (b) the correction and prevention of hypercholesterolemia. These aims are achieved by having these young patients take diets high in carbohydrate —300 to 400 gm—high in protein and low in fat—not in excess of 50 gm—with appropriate insulin therapy.

## PROGRESS OF THE JUVENILE DIABETIC—FACTS AND PRINCIPLES

The juvenile diabetic is brought face to face with responsibilities of the adult. Despite the best of intentions and efforts of all concerned a barrier or modifying influence conditions his activities somewhat and as a result the occasional child becomes introspective, moody and emotionally unstable. A sympathetic understanding with good disciplinary training on the part of the wise parent dissipates the child's frustration and makes him the key person on the team—the patient, parents and physician. With adolescence and maturity his better than average intelligence works in his favor—situations are easier to handle, his ego is less sensitive and he develops self-confidence. Instead of feeling restricted and hemmed in by the differences which exist between him and other children he begins, with or before adolescence, to accept responsibilities. The acceptance of responsi-

* Oreton (Ciba), 25 mg two or three times weekly for two or three years.

bility when the adolescent gets his first position and earns his first money, or when he or she falls in love or experiences some other maturing influence, has a favorable influence on the control of the diabetes

Finally, a normal approach to marriage and parenthood is encouraged with an understanding of the part played by heredity in causing diabetes and of the special care necessary during pregnancy if it is to come to a successful conclusion

TABLE 40

DIABETES IN CHILDREN CONTRASTED WITH DIABETES OCCURRING IN ADULTS

| | CHILDREN | ADULTS |
|---|---|---|
| Onset | Abrupt | Usually gradual |
| Weight | Normal | *Approximately 70 per cent are overweight* |
| Stability | Diabetes labile | Diabetes usually relatively stable |
| Insulin | *Necessary for all* | *Approximately ⅓ must take insulin* |
| Coma | Relatively *frequent* | *Infrequent* |
| Sensitivity to Minor Changes | Very sensitive | Relatively insensitive |
| Family History of Diabetes | Very common | Common |
| Degenerative Changes | Infrequent | Common |
| Hepatomegaly | Common | Relatively uncommon |
| Control of Diabetes | Difficult | Easy |
| Control of Food Intake | Difficult | Relatively easy |
| Variations of Activity | Great | Small |

## OUTLOOK FOR THE JUVENILE DIABETIC

The outlook for the juvenile diabetic is excellent in contrast with that of the pre insulin era Diabetic children, wisely treated, grow in a normal manner They do better than the average student in school Professional or other independent careers are encouraged, thereby circumventing or reducing the possibilities of being refused employment because of the diabetes Ordinarily, diabetic individuals do well at any occupation but it is unwise for them to be exposed to power driven machinery and equally unwise to select a position or profession which by its nature entails irregular living, meals physical activities and traveling, e g, a diabetic who becomes a physician should not practice obstetrics or do general practice but institutional work, permitting regularity of meals and hours, would be quite satisfactory

## REFERENCES

1 Pincus G and White G Am J M Sc 186 1 1933
2 White P In Treatment of Diabetes Mellitus by E P Joslin and associates Lea & Febiger Co., Philadelphia 1946 p 760

# Appendix

HEIGHTS AND WEIGHTS OF CHILDREN BETWEEN ONE AND FOUR YEARS OF AGE (WITHOUT CLOTHES)[1]

| 5602 Boys | | Age, Months | 4821 Girls | |
|---|---|---|---|---|
| Height, Inches | Weight, Pounds | | Height, Inches | Weight, Pounds |
| 26.5 | 18.0 | 6 | 25.9 | 16.8 |
| 27.3 | 19.1 | 7 | 26.5 | 17.4 |
| 27.6 | 19.8 | 8 | 27.0 | 18.3 |
| 28.1 | 20.4 | 9 | 27.6 | 19.1 |
| 28.5 | 20.9 | 10 | 27.9 | 19.5 |
| 29.0 | 21.4 | 11 | 28.4 | 20.1 |
| 29.4 | 21.9 | 12 | 28.9 | 20.8 |
| 29.9 | 22.9 | 13 | 29.4 | 21.0 |
| 30.3 | 23.0 | 14 | 29.5 | 21.6 |
| 30.8 | 23.6 | 15 | 30.1 | 21.9 |
| 31.1 | 24.1 | 16 | 30.5 | 22.0 |
| 31.4 | 24.3 | 17 | 30.8 | 22.9 |
| 31.8 | 24.6 | 18 | 31.1 | 23.4 |
| 32.3 | 25.5 | 19 | 31.5 | 23.8 |
| 32.6 | 25.8 | 20 | 32.0 | 24.1 |
| 32.9 | 25.8 | 21 | 32.3 | 24.8 |
| 33.3 | 26.9 | 22 | 32.6 | 25.3 |
| 33.6 | 27.0 | 23 | 32.9 | 25.6 |
| 33.8 | 27.1 | 24 | 33.4 | 26.4 |
| 34.0 | 27.9 | 25 | 33.8 | 26.9 |
| 34.1 | 28.3 | 26 | 33.9 | 27.3 |
| 34.8 | 29.0 | 27 | 33.9 | 27.3 |
| 35.1 | 29.1 | 28 | 34.6 | 27.8 |
| 35.4 | 29.3 | 29 | 34.8 | 27.8 |
| 35.4 | 29.5 | 30 | 34.9 | 28.3 |
| 35.3 | 30.3 | 31 | 35.1 | 28.8 |
| 36.0 | 30.6 | 32 | 35.4 | 29.0 |
| 36.1 | 30.6 | 33 | 35.6 | 29.1 |
| 36.5 | 31.1 | 34 | 36.3 | 30.1 |
| 36.8 | 31.9 | 35 | 36.5 | 30.3 |
| 37.1 | 32.3 | 36 | 36.8 | 30.5 |
| 37.4 | 32.3 | 37 | 36.9 | 30.8 |
| 37.5 | 32.4 | 38 | 37.0 | 31.0 |
| 37.9 | 33.1 | 39 | 37.3 | 31.6 |
| 38.4 | 33.5 | 40 | 37.5 | 32.0 |
| 38.6 | 33.6 | 41 | 37.8 | 32.3 |
| 38.6 | 33.8 | 42 | 38.0 | 32.5 |
| 38.8 | 33.8 | 43 | 38.3 | 32.8 |
| 38.9 | 34.3 | 44 | 38.5 | 33.0 |
| 39.0 | 34.5 | 45 | 38.5 | 33.5 |
| 39.0 | 34.8 | 46 | 38.8 | 33.5 |
| 39.3 | 33.8 | 47 | 38.9 | 33.5 |
| 39.5 | 35.9 | 48 | 39.0 | 33.8 |

[1] Crum, F. S. Quarterly Publication of the American Statistical Association, Boston, September, 1916, N.S., No. 115, p. 332.

Height—Weight—Age Table (Boys)

| Height Inches | 5 Yrs | 6 Yrs | 7 Yrs | 8 Yrs | 9 Yrs | 10 Yrs | 11 Yrs | 12 Yrs | 13 Yrs | 14 Yrs | 15 Yrs | 16 Yrs | 17 Yrs | 18 Yrs | 19 Yrs |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 38 | 34 | 34 | | | | | | | | | | | | | |
| 39 | 35 | 35 | | | | | | | | | | | | | |
| 40 | 36 | 36 | | | | | | | | | | | | | |
| 41 | 38 | 38 | 38 | | | | | | | | | | | | |
| 42 | 39 | 39 | 39 | 39 | | | | | | | | | | | |
| 43 | 41 | 41 | 41 | 41 | | | | | | | | | | | |
| 44 | 44 | 44 | 44 | 44 | | | | | | | | | | | |
| 45 | 46 | 46 | 46 | 46 | 46 | | | | | | | | | | |
| 46 | 47 | 48 | 48 | 48 | 48 | | | | | | | | | | |
| 47 | 49 | 50 | 50 | 50 | 50 | 50 | | | | | | | | | |
| 48 | | 52 | 53 | 53 | 53 | 53 | | | | | | | | | |
| 49 | | 55 | 55 | 55 | 55 | 55 | 55 | | | | | | | | |
| 50 | | 57 | 58 | 58 | 58 | 58 | 58 | 58 | | | | | | | |
| 51 | | | 61 | 61 | 61 | 61 | 61 | 61 | | | | | | | |
| 52 | | | 63 | 64 | 64 | 64 | 64 | 64 | 64 | | | | | | |
| 53 | | | 66 | 67 | 67 | 67 | 67 | 68 | 68 | | | | | | |
| 54 | | | | 70 | 70 | 70 | 70 | 71 | 71 | 72 | | | | | |
| 55 | | | | 72 | 72 | 73 | 73 | 74 | 74 | 74 | | | | | |
| 56 | | | | 75 | 76 | 77 | 77 | 77 | 78 | 78 | 80 | | | | |
| 57 | | | | | 79 | 80 | 81 | 81 | 82 | 83 | 83 | | | | |
| 58 | | | | | 83 | 84 | 84 | 85 | 85 | 86 | 87 | | | | |
| 59 | | | | | | 87 | 88 | 89 | 89 | 90 | 90 | 90 | | | |
| 60 | | | | | | 91 | 92 | 92 | 93 | 94 | 95 | 96 | | | |
| 61 | | | | | | | | | | | | | | | |
| 62 | | | | | | | | | | | | | | | |
| 63 | | | | | | | | | | | | | | | |
| 64 | | | | | | | | | | | | | | | |
| 65 | | | | | | | | | | | | | | | |
| 66 | | | | | | | | | | | | | | | |
| 67 | | | | | | | | | | | | | | | |
| 68 | | | | | | | | | | | | | | | |
| 69 | | | | | | | | | | | | | | | |
| 70 | | | | | | | | | | 143 | 144 | 145 | 148 | 151 | 155 |
| 71 | | | | | | | | | | 148 | 150 | 151 | 152 | 154 | 159 |
| 72 | | | | | | | | | | | 153 | 155 | 156 | 158 | 163 |
| 73 | | | | | | | | | | | 157 | 160 | 162 | 164 | 167 |
| 74 | | | | | | | | | | | 160 | 164 | 168 | 170 | 171 |

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HEIGHT—WEIGHT—AGE TABLE GIRLS

| Height, Inches | 5 Yrs | 6 Yrs | 7 Yrs | 8 Yrs | 9 Yrs | 10 Yrs | 11 Yrs | 12 Yrs | 13 Yrs | 14 Yrs | 15 Yrs | 16 Yrs | 17 Yrs | 1 Y |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 38 | 33 | 33 | | | | | | | | | | | | |
| 39 | 34 | 34 | | | | | | | | | | | | |
| 40 | 36 | 36 | 36 | | | | | | | | | | | |
| 41 | 37 | 37 | 37 | | | | | | | | | | | |
| 42 | 39 | 39 | 39 | | | | | | | | | | | |
| 43 | 41 | 41 | 41 | 41 | | | | | | | | | | |
| 44 | 42 | 42 | 42 | 42 | | | | | | | | | | |
| 45 | 45 | 45 | 45 | 45 | 45 | | | | | | | | | |
| 46 | 47 | 47 | 47 | 48 | 48 | | | | | | | | | |
| 47 | 49 | 50 | 50 | 50 | 50 | 50 | | | | | | | | |
| 48 | | 52 | 52 | 52 | 52 | 53 | 53 | | | | | | | |
| 49 | | 54 | 54 | 55 | 55 | 56 | 56 | | | | | | | |
| 50 | | 56 | 56 | 57 | 58 | 59 | 61 | 62 | | | | | | |
| 51 | | | 59 | 60 | 61 | 62 | 63 | 65 | | | | | | |
| 52 | | | 63 | 64 | 64 | 64 | 65 | 67 | | | | | | |
| 53 | | | 66 | 67 | 67 | 68 | 68 | 69 | 71 | | | | | |
| 54 | | | | 69 | 70 | 70 | 71 | 71 | 73 | | | | | |
| 55 | | | | 72 | 74 | 74 | 74 | 75 | 77 | 78 | | | | |
| 56 | | | | | 76 | 78 | 78 | 79 | 81 | 83 | | | | |
| 57 | | | | | 80 | 82 | 82 | 82 | 84 | 88 | 92 | | | |
| 58 | | | | | | 84 | 86 | 86 | 88 | 93 | 96 | 101 | | |
| 59 | | | | | | 87 | 90 | 90 | 92 | 96 | 100 | 103 | 104 | |
| 60 | | | | | | 91 | 95 | 95 | 97 | 101 | 105 | 108 | 109 | 11 |
| 61 | | | | | | | 99 | 100 | 101 | 105 | 108 | 112 | 113 | 11 |
| 62 | | | | | | | 104 | 105 | 106 | 109 | 113 | 115 | 117 | 11 |
| 63 | | | | | | | | 110 | 110 | 112 | 116 | 117 | 119 | 12 |
| 64 | | | | | | | | 114 | 115 | 117 | 119 | 120 | 122 | 12 |
| 65 | | | | | | | | 118 | 120 | 121 | 122 | 123 | 125 | 12 |
| 66 | | | | | | | | | 124 | 124 | 125 | 128 | 129 | 13 |
| 67 | | | | | | | | | 128 | 130 | 131 | 131 | 133 | 13 |
| 68 | | | | | | | | | 131 | 133 | 135 | 136 | 138 | 13 |
| 69 | | | | | | | | | | 135 | 137 | 138 | 140 | 14 |
| 70 | | | | | | | | | | 136 | 138 | 140 | 142 | 14 |
| 71 | | | | | | | | | | 138 | 140 | 142 | 144 | 14 |

Prepared by Bird T. Baldwin, Ph.D., and Thomas D. Wood, M.D.

HEIGHT—WEIGHT—AGE TABLE (BOYS)

| Height Inches | 5 Yrs | 6 Yrs | 7 Yrs | 8 Yrs | 9 Yrs | 10 Yrs | 11 Yrs | 12 Yrs | 13 Yrs | 14 Yrs | 15 Yrs | 16 Yrs | 17 Yrs | 18 Yrs | 19 Yrs |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 38 | 34 | 34 | | | | | | | | | | | | | |
| 39 | 35 | 35 | | | | | | | | | | | | | |
| 40 | 36 | 36 | | | | | | | | | | | | | |
| 41 | 38 | 38 | 38 | | | | | | | | | | | | |
| 42 | 39 | 39 | 39 | 39 | | | | | | | | | | | |
| 43 | 41 | 41 | 41 | 41 | | | | | | | | | | | |
| 44 | 44 | 44 | 44 | 44 | | | | | | | | | | | |
| 45 | 46 | 46 | 46 | 46 | 46 | | | | | | | | | | |
| 46 | 47 | 48 | 48 | 48 | 48 | | | | | | | | | | |
| 47 | 49 | 50 | 50 | 50 | 50 | 50 | | | | | | | | | |
| 48 | | 52 | 53 | 53 | 53 | 53 | | | | | | | | | |
| 49 | | 55 | 55 | 55 | 55 | 55 | 55 | | | | | | | | |
| 50 | | 57 | 58 | 58 | 58 | 58 | 58 | 58 | | | | | | | |
| 51 | | | 61 | 61 | 61 | 61 | 61 | 61 | | | | | | | |
| 52 | | | 63 | 64 | 64 | 64 | 64 | 64 | 64 | | | | | | |
| 53 | | | 66 | 67 | 67 | 67 | 67 | 68 | 68 | | | | | | |
| 54 | | | | 70 | 70 | 70 | 70 | 71 | 71 | 72 | | | | | |
| 55 | | | | 72 | 72 | 73 | 73 | 74 | 74 | 74 | | | | | |
| 56 | | | | 75 | 76 | 77 | 77 | 77 | 78 | 78 | 80 | | | | |
| 57 | | | | | 79 | 80 | 81 | 81 | 82 | 83 | 83 | | | | |
| 58 | | | | | 83 | 84 | 84 | 85 | 85 | 86 | 87 | | | | |
| 59 | | | | | | 87 | 88 | 89 | 89 | 90 | 90 | 90 | | | |
| 60 | | | | | | 91 | 92 | 92 | 93 | 94 | 95 | 96 | | | |
| 61 | | | | | | | | | | | | | | | |
| 62 | | | | | | | | | | | | | | | |
| 63 | | | | | | | | | | | | | | | |
| 64 | | | | | | | | | | | | | | | |
| 65 | | | | | | | | | | | | | | | |
| 66 | | | | | | | | | | | | | | | |
| 67 | | | | | | | | | | | | | | | |
| 68 | | | | | | | | | | | | | | | |
| 69 | | | | | | | | | | | | | | | |
| 70 | | | | | | | | | | 143 | 144 | 145 | 148 | 151 | 155 |
| 71 | | | | | | | | | | 148 | 150 | 151 | 152 | 154 | 159 |
| 72 | | | | | | | | | | | 153 | 155 | 156 | 158 | 163 |
| 73 | | | | | | | | | | | 157 | 160 | 162 | 164 | 167 |
| 74 | | | | | | | | | | | 160 | 164 | 168 | 170 | 171 |

Prepared by Bird T Baldwin Ph D and Thomas D Wood M D

Height—Weight—Age Table (Girls)

| Height Inches | 5 Yrs | 6 Yrs | 7 Yrs | 8 Yrs | 9 Yrs | 10 Yrs | 11 Yrs | 12 Yrs | 13 Yrs | 14 Yrs | 15 Yrs | 16 Yrs | 17 Yrs | 18 Yrs |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 38 | 33 | 33 | | | | | | | | | | | | |
| 39 | 34 | 34 | | | | | | | | | | | | |
| 40 | 36 | 36 | 36 | | | | | | | | | | | |
| 41 | 37 | 37 | 37 | | | | | | | | | | | |
| 42 | 39 | 39 | 39 | | | | | | | | | | | |
| 43 | 41 | 41 | 41 | 41 | | | | | | | | | | |
| 44 | 42 | 42 | 42 | 42 | | | | | | | | | | |
| 45 | 45 | 45 | 45 | 45 | 45 | | | | | | | | | |
| 46 | 47 | 47 | 47 | 48 | 48 | | | | | | | | | |
| 47 | 49 | 50 | 50 | 50 | 50 | 50 | | | | | | | | |
| 48 | | 52 | 52 | 52 | 52 | 53 | 53 | | | | | | | |
| 49 | | 54 | 54 | 55 | 55 | 56 | 56 | | | | | | | |
| 50 | | 56 | 56 | 57 | 58 | 59 | 61 | 62 | | | | | | |
| 51 | | | 59 | 60 | 61 | 61 | 63 | 65 | | | | | | |
| 52 | | | 63 | 64 | 64 | 64 | 65 | 67 | | | | | | |
| 53 | | | 66 | 67 | 67 | 68 | 68 | 69 | 1 | | | | | |
| 54 | | | | 69 | 70 | 70 | 71 | 71 | 73 | | | | | |
| 55 | | | | 72 | 74 | 74 | 74 | 75 | 77 | 78 | | | | |
| 56 | | | | | 76 | 78 | 78 | 79 | 81 | 83 | | | | |
| 57 | | | | | 80 | 82 | 82 | 92 | 84 | 88 | 92 | | | |
| 58 | | | | | | 84 | 86 | 86 | 88 | 93 | 96 | 101 | | |
| 59 | | | | | | 87 | 90 | 90 | 92 | 96 | 100 | 103 | 104 | |
| 60 | | | | | | 91 | 95 | 95 | 97 | 101 | 105 | 108 | 109 | 111 |
| 61 | | | | | | | 99 | 100 | 101 | 105 | 108 | 112 | 113 | 116 |
| 62 | | | | | | | 104 | 105 | 106 | 109 | 113 | 115 | 117 | 118 |
| 63 | | | | | | | | 110 | 110 | 112 | 116 | 117 | 119 | 120 |
| 64 | | | | | | | | 114 | 115 | 117 | 119 | 120 | 122 | 123 |
| 65 | | | | | | | | 118 | 120 | 121 | 122 | 123 | 125 | 126 |
| 66 | | | | | | | | | 124 | 124 | 125 | 128 | 129 | 130 |
| 67 | | | | | | | | | 128 | 130 | 131 | 133 | 133 | 135 |
| 68 | | | | | | | | | 131 | 133 | 135 | 136 | 138 | 138 |
| 69 | | | | | | | | | | 135 | 137 | 138 | 140 | 142 |
| 70 | | | | | | | | | | 136 | 138 | 140 | 142 | 144 |
| 71 | | | | | | | | | | 138 | 140 | 142 | 144 | 145 |

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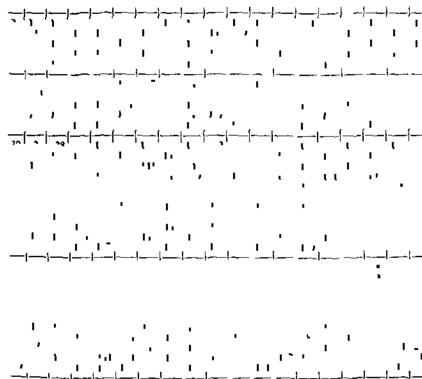
HEIGHTS AND WEIGHTS OF 136,504 WOMEN FIFTEEN OR MORE YEARS OF AGE (WITH CLOTHES)[1]

| Age | Graded average Weight in Pounds with Clothes | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Feet and Inches with Shoes | | | | | | | | | | | | | | | | |
| | 4-8 | 4-9 | 4-10 | 4-11 | 5-0 | 5-1 | 5-2 | 5-3 | 5-4 | 5-5 | 5-6 | 5-7 | 5-8 | 5-9 | 5-10 | 5-11 | 6-0 |
| 55 | 125 | 127 | 129 | 131 | 133 | 135 | 138 | 141 | 144 | 148 | 153 | 158 | 163 | 167 | 172 | 174 | 177 |

[1] Association of Life Insurance Directors and Actuarial Society of America New York, 1912 p 67 Published by a committee Allow 1½ inches for shoes and 6 pounds for clothes

HEIGHTS AND WEIGHTS OF 221 819 MEN FIFTEEN OR MORE YEARS OF AGE (WITH CLOTHES

| Age | Graded Average Weight in Pounds with Clothes | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Feet and Inches with Shoes | | | | | | | | | | | | | | | | | |
| | 5-0 | 5 1 | 5 2 | 5 3 | 5-4 | 5 5 | 5-6 | 5 7 | 5 8 | 5-9 | 5 10 | 5 11 | 6-0 | 6-1 | 6-2 | 6-3 | 6-4 | 6- |



| | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 55 | 135 | 137 | 139 | 142 | 145 | 149 | 153 | 158 | 163 | 168 | 173 | 178 | 184 | 191 | 198 | 205 | 212 | 21 |

[1] Association of Life Insurance Directors and Actuarial Society of America New York 191
p 38 Published by a committee Allow 1 inch for shoes and 10 pounds for clothes

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